United States Patent [19]

Warner, Jr. et al.

[11] **4,191,767**

[45] **Mar. 4, 1980**

[54] **METHOD FOR TREATING FUNGAL INFECTION IN MAMMALS WITH IMIDAZO [1,2-A]QUINOXALINES**

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[73] Assignee: **Westwood Pharmaceuticals, Inc.**, Buffalo, N.Y.

[21] Appl. No.: **858,513**

[22] Filed: **Dec. 8, 1977**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 757,640, Jan. 7, 1977, abandoned.

[51] **Int. Cl.**[2] **A01N 9/22; C07D 487/04**

[52] **U.S. Cl.** **424/250**; 544/346

[58] **Field of Search** 424/250; 544/346

[56] **References Cited**

PUBLICATIONS

Lunkenheimer et al. Chem. Abs., 82, 156379j (1975).

Primary Examiner—Mark L. Berch

Attorney, Agent, or Firm—Morton S. Simon; Irving Holtzman

[57] **ABSTRACT**

A method for treating a fungal infection in mammals which comprises administering to said mammals having a fungal infection a therapeutically effective amount of a 4-(substituted phenyl)imidazo[1,2-a]quinoxaline.

2 Claims, No Drawings

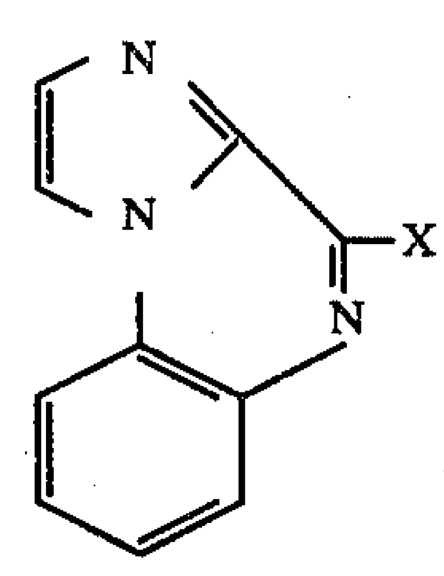
METHOD FOR TREATING FUNGAL INFECTION IN MAMMALS WITH IMIDAZO [1,2-A]QUINOXALINES

RELATED CASES

This is a continuation-in-part of application Ser. No. 757,640 filed Jan. 7, 1977, now abandoned.

This invention relates to certain 4-substituted imidazo[1,2-a]quinoxalines and to processes for preparing the same. It also concerns certain 1-(2-acylaminophenyl-)imidazoles which among other things are useful as intermediates in the preparation of 4-substituted imidazo[1,2-a]quinoxalines. The aforesaid compounds are useful for a variety of purposes which will be described in more detail below. Some of these are useful as immunosuppressants; whereas, others are useful as anti-inflammatory agents or display antifungal activity. Moreover, some exhibit two or all three of these activities.

The 4-substituted imidazo[1,2-a]quinoxalines encompassed in the present invention may be described by the formula:



I

and pharmaceutically acceptable salts thereof wherein X is —R^1 or —NHR^2 wherein:

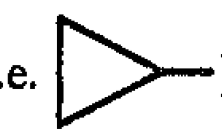
(1) R^1 is bonded to a ring carbon by a carbon-to-carbon linkage and is an aliphatic, cycloaliphatic, substituted phenyl, fused bicyclic aryl; or monocyclic aryl-substituted aliphatic; and

(2) R^2 is a radical bonded to a nitrogen by a carbon to nitrogen linkage; said radical being selected from the group consisting of aliphatic, cycloaliphatic, phenyl, substituted phenyl, fused bicyclic aryl or a monocyclic aryl-substituted aliphatic group.

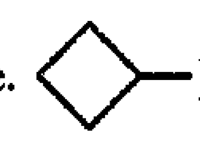
When R^1 is an aliphatic group, it may be a straight chain or branched chain hydrocarbon group which is saturated, monounsaturated or polyunsaturated. It may also comprise a straight chain or branched chain group containing other than carbon-to-carbon bondings e.g. ether linkages, carbon to halogen linkages, etc. Ordinarily, it will contain from about 1 to 18 carbon atoms, the most typical radicals of this group being the alkyl radicals having from 1 to 18 carbon atoms.

By way of illustrating the aliphatic groups that may be represented by R^1, the following are given: CH_3—; CH_3CH_2—; CH_3CH_2—CH_2—; $CH_3(CH_2)_n$— in which n is 3, 4, 5, 6, 7, 8, 14 and 16 respectively; $(CH_3)_2CH$—CH_2—; $CH_3(CH_2)_3(CH_3CH_2)CH$—, CH_2=CH—$(CH_2)_8$—, alkoxyalkyl in which the alkyl moieties have from 1 to 4 carbon atoms e.g. methoxymethyl; halogenoalkyl (i.e. CH_2Cl—; CH_3CHCl—; $CHCL_2$—; CCl_3—; CH_2Br—; CF_3).

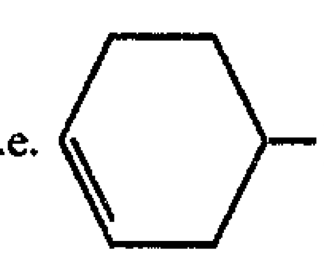
When R^1 is a cycloaliphatic radical it will most often be a cycloalkyl radical containing 3 to 8 carbon atoms or a cycloalkenyl radical containing 5 to 6 carbon atoms. By way of illustrating the cycloaliphatic radicals that may correspond to R^1 in formula I mention may be made of the cyclopropyl

(i.e. );

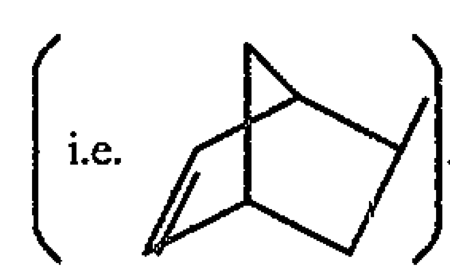
cyclobutyl

(i.e. );

cyclohexyl, cyclohexenyl

(i.e. );

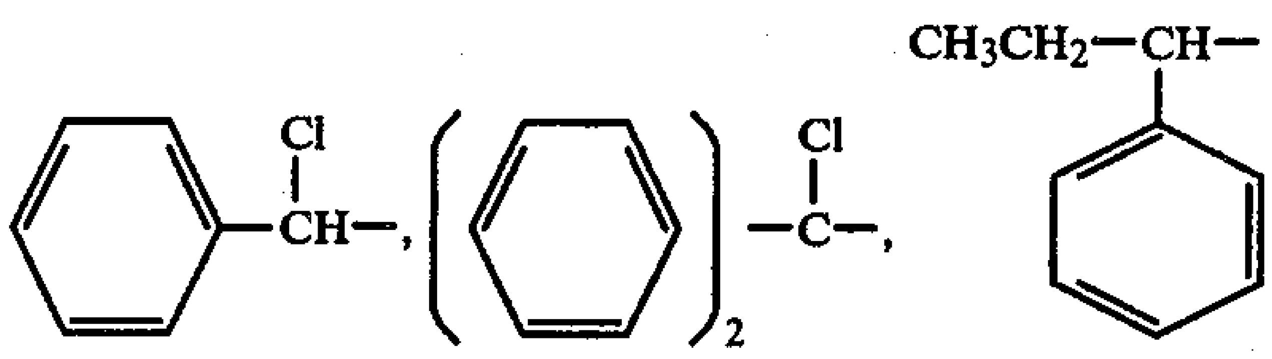
and norbornenyl



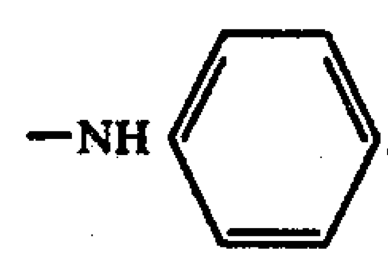
When R^1 is a substituted phenyl radical in formula I above, the phenyl group may have from 1 to 5 substituents but will usually be mono, di or trisubstituted. Typical among the groups that may be contained in the phenyl group are (a) alkyl groups which are branched or straight chain containing 1 to 6 carbon atoms e.g. methyl, ethyl, tertiary butyl; (b) alkoxyl groups containing 1 to 6 carbon atoms e.g. methoxy, ethoxy; (c) hydroxy; (d) acyloxy containing 1 to 18 carbon atoms; (e) halogen e.g. 1 or 2 Cl, F, Br, I preferably in the meta and/or para position; (f) nitro; (g) amino; (h) acylamino in which the acylamino moiety is derived from an alkanoic acid containing 1 to 18 carbon atoms and benzamides in which the benzene ring is unsubstituted or monosubstituted, disubstituted or trisubstituted with alkyl groups containing 1 to 5 carbon atoms or halogen atoms; (i) polyhydroxyalkylamino groups containing 4 to 8 carbon atoms; (j) cyano; (k) trifluoromethyl; (l) mercapto; (m) alkylthio; (n) acylthio containing 1 to 18 carbon atoms; (o) carboxyl; (p) carboalkoxyl containing 1 to 8 aliphatic carbon atoms; (q) phenyl; (r) phenoxy, and combinations thereof.

When R^1 is a fused bicyclic aryl radical, it may be a substituted or unsubstituted radical. These are exemplified by such fused bicyclic hydrocarbon radicals as 1-naphtyl, 2-naphthyl etc.

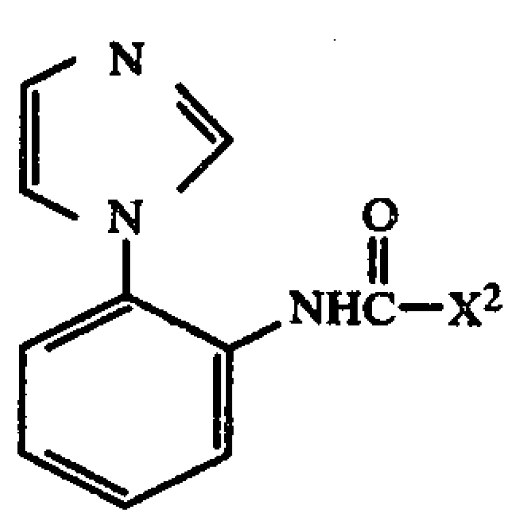
When R^1 is a monocyclic aryl substituted aliphatic radical, the monocyclic aryl moiety may be either of the substituted or unsubstituted variety. The aliphatic moiety of this group may be either of the saturated or unsaturated straight chain or branched chain hydrocarbon variety or it may contain other than carbon-to-carbon bonding. This may be illustrated by such groups as phenoxymethyl; benzyl, styryl,



The group R^2 in the radical $-NHR^2$ of formula I above is exemplified by the same radicals given above in illustrating the radical $-R^1$. In addition, R^2 may also be phenyl as in the case of the group



In general, the compounds included in formula I above as well as the cases in formula I in which X is hydrogen or phenyl may be prepared by heating the corresponding 1-(2-acylaminophenyl)imidazole at reflux in the presence of cyclizing quantities of a cyclizing agent e.g. polyphosphoric acid or phosphorous oxychloride, etc. for sufficient time to cause significant cyclization of this reactant. More particularly, the 1-(2-acylaminophenyl)imidazole reactants that can be employed in this process may be described by the general formula:



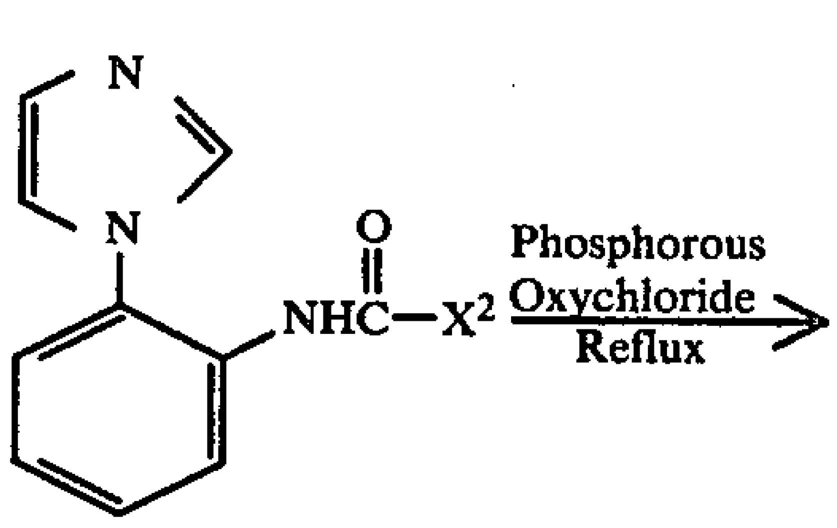
II

in which X^2 is R^5 or $—NHR^2$ wherein: R^5 is hydrogen or an aliphatic, cycloaliphatic, phenyl or substituted phenyl, fused bicyclic aryl or monocyclic aryl substituted aliphatic radical and R^2 has the same values assigned to it in connection with formula I above.

The group R^5 in formula II is illustrated by the same groups that illustrate R^1 in formula I. However, in addition, R^5 may also be illustrated by the phenyl radical.

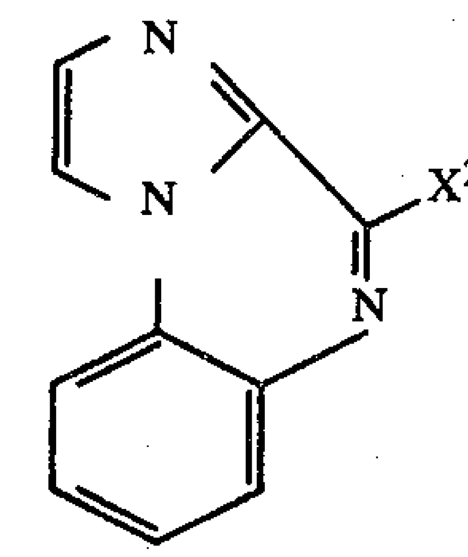
The reaction can be depicted by the following equation:

III



II

-continued



IV

The process of equation III is preferably carried out in the presence of an excess of an organic amine solvent. A variety of solvents may be used for this purpose among which mention may be made of the following: pyridine, 2,6-dimethylpyridine, N,N-dimethylaniline, trimethylamine, and N-methylmorpholine, etc. However, the preferred organic solvent is pyridine.

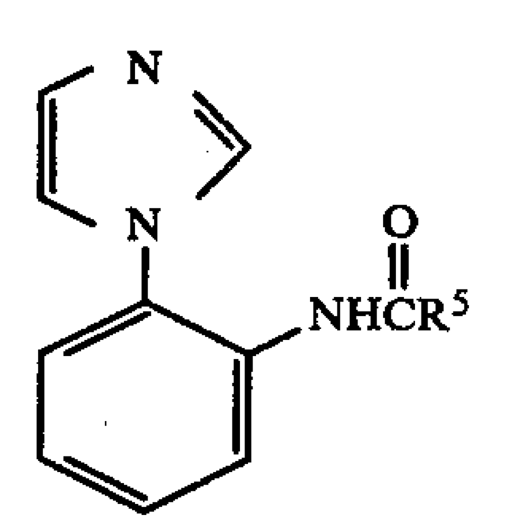
The quantity of phosphorous oxychloride that is employed in the reaction can vary somewhat. Generally, however, the phosphorous oxychloride will be employed in the range of from about one-half mole to about 6 moles and preferably one-half mole to two moles per mole of compound II.

The desired product IV may be recovered from the reaction mixture using any of the ordinary techniques well known to those skilled in this art. The time of reaction will vary depending upon, among other things, the particular reactants or molar quantities of reactants employed. In general, the reaction time will be from about 30 to 120 minutes.

The temperature employed in carrying out the reaction will also vary depending upon the particular reactants selected, the solvent and other factors. Ordinarily, the temperature employed will be the reflux temperature of the reaction mixture. This generally will be in the range of from about 95° C. to 195° C.

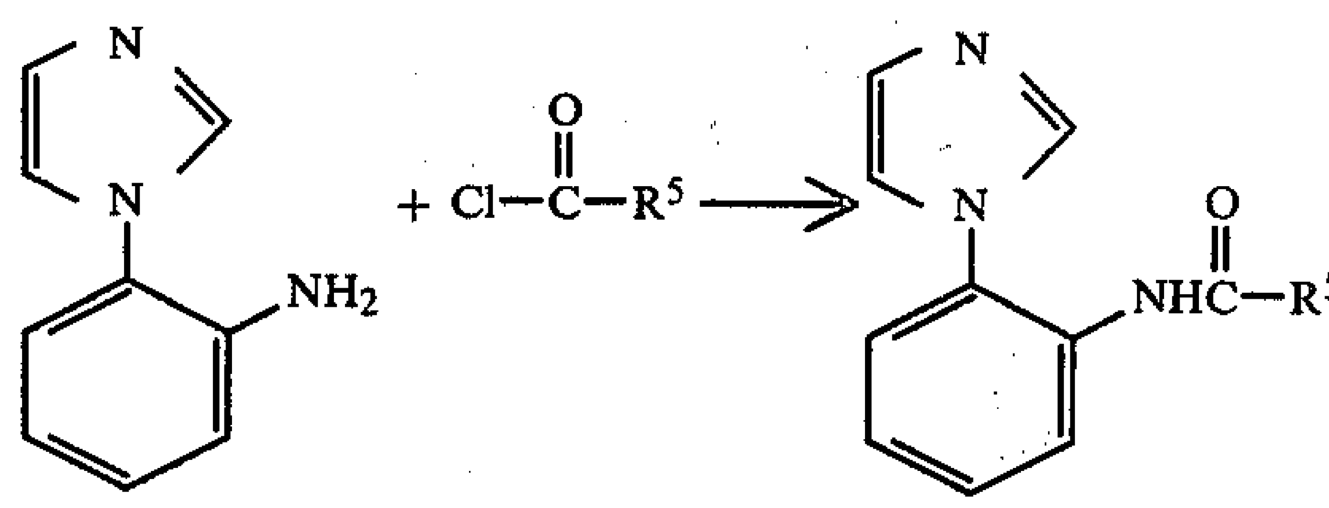
The method of preparing the 1-(2-acylaminophenyl)imidazoles (compound II) will vary depending on the particular type that is being made. Thus, for example, in preparing compound of the general type:

V



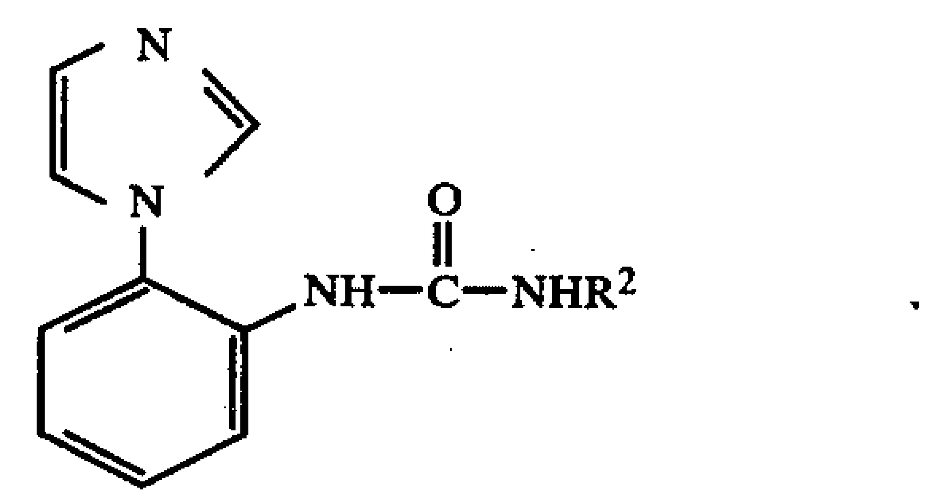
where R^5 is hydrogen, aliphatic, cycloaliphatic, phenyl, substituted phenyl, fused bicyclic aryl or monocyclic aryl substituted aliphatic group, the 1-(2-acylaminophenyl)imidazole is reacted with the appropriate acid halide e.g. the acid chloride.

This can be expressed by the following equation:

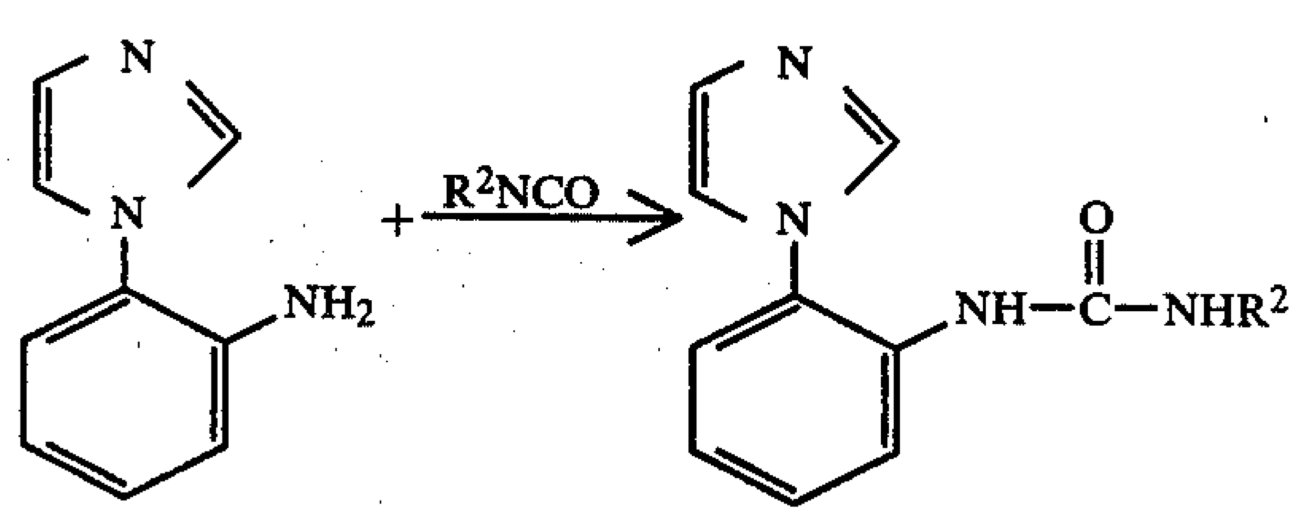

VI

in which R^5 has the value ascribed to it above. The reaction will usually be carried out employing equimolar amounts of the appropriate acid chloride and in the presence of excess solvent (e.g. pyridine) at reflux.

When the compounds in question are of the phenylureylene type e.g.


VII

where R^2 is hydrogen, aliphatic, cycloaliphatic, phenyl, substituted phenyl, fused bicyclic aryl or monocyclic aryl substituted aliphatic group, these are prepared by reacting the aminophenylimidazole with the appropriate isocyanate. This can be expressed by the following equation:


VIII

in which R^2 has the value ascribed to it above. This reaction is preferably carried out in the presence of a solvent and at steam bath temperatures. A typical solvent that can be employed is toluene and the reactants are usually used in about equimolar quantities. The products obtained from reactions VI and VIII may be recovered using standard techniques well known to those skilled in this art.

Prior Art

U.S. Pat. No. 3,887,566 discloses imidazo[1,2-a]quinoxaline and 4-phenylimidazo[1,2-a]quinoxaline. However, this reference does not disclose the 4-substituted imidazo[1,2-a]quinoxalines of the present invention nor the process for making these compounds. The activity disclosed in this reference for these compounds is as cardiovascular drugs. There is no disclosure of the fact that these compounds may have immunosuppressant activity, antifungal activity or non-steroidal anti-inflammatory action. It is in fact interesting to note that the unsubstituted imidazo[1,2-a]quinoxaline lacks immunosuppressant activity while the 4-phenylimidazo[1,2-a]quinoxaline has only minor activity which is greatly increased by substitution on the para- and meta- positions on the benzene ring.

Uryukina et al, Khim. Geterotsikl. Soedin., 1972, 1558–60 (See C.A. 78, 58345^t (1973) discloses the unsubstituted and the 7-methyl, methoxy, and bromo substituted imidazo[1,2-a]quinoxalines. No 4-substituted products are disclosed nor is any utility disclosed for these compounds.

Kovalev et al, Farmakol. Toksilkol (Moscow), 36 (2), 232–238, 1973 (See C.A. 78 154693^a) also discloses the 7-methoxyimidazo[1,2-a]quinoxaline and suggests the use of this material as an hypotensive agent. This reference likewise does not disclose the 4-substituted imidazo[1,2-a]quinoxalines of the present invention or their utility.

Japanese Patents 10677/74 and 10678/74 disclose certain 4-substituted 1,2-dihydroimidazo[1,2-a]quinoxalines and the fact that these materials are useful as anti-inflammatory agents. These references do not show the unhydrogenated compounds of this invention. Moreover, no immunosuppressant activity or antifungal activity is disclosed.

Siminov et al, Khim. Geterotsikl, Soedin, 7, 570 (1971) (See C.A. 76, 25242^n 1972) discloses a process for synthesizing imidazo[1,2-a]quinoxaline involving the reduction of 1-(o-nitrophenyl)-2-formylimidazole. This is obviously not related to the process of the present invention.

The following Examples are given to further illustrate the present invention. It is to be understood, however, that they are not limitative of this invention.

The compounds described in the Tables below were prepared as described. Melting points were obtained by the capillary tube method using a Mel-Temp melting point apparatus and are uncorrected. Ultraviolet spectra were obtained in ethanol solution using a Beckman U.V. Acta III or a Beckman DBG. 1-(2-aminophenyl-)imidazole was prepared as reported by A. F. Pozharskii, A. M. Siminov and L. M. Sitkina, Khim. Geterotskl. Soedin. 5, 1916 (1969) [Chem. Abstr., 72 11427^a (1970)].

Table I below further illustrates the preparation of the aliphatic, cycloaliphatic and monocyclic aryl substituted aliphatic- amidophenylimidazoles of the present invention. Table II further exemplifies the preparation of the aryl (including the fused ring aryl) amidophenylimidazoles of this invention.

Except as noted in Tables I and II, the amides were prepared by reacting equimolar amounts of the appropriate acid chloride with 1-(2-aminophenyl)imidazole in the presence of excess pyridine on a steam bath for 45 minutes. The reaction mixture was then stirred into ice water and the crude product isolated according to one of the following methods.

Method A

If a solid was obtained, it was directly crystallized from the solvent indicated in Table I.

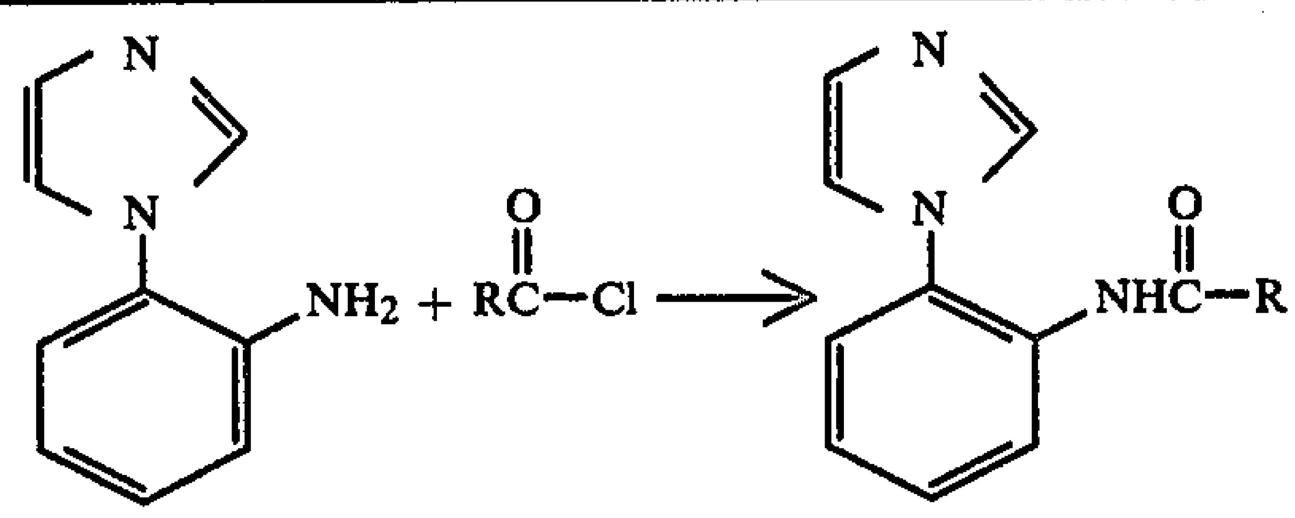
Method B

If an oil was obtained, it was dissolved in a minimum amount of chloroform and passed through an alumina column with the amount of alumina being approximately twenty times the weight of the crude solid; elution was with chloroform. The chloroform was evaporated from the crude product which was crystallized as indicated in Table I.

Method C

If a solution was obtained in the ice water mixture, the pyridine/water azeotrope was removed until the crude product separated. It was then treated as in Method B above.

TABLE I



1-(2-alkanamidophenyl)imidazoles

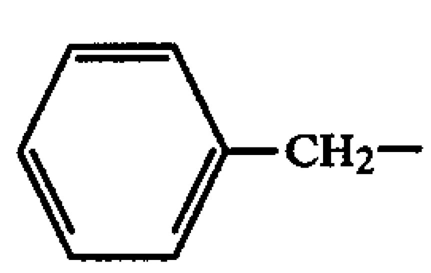
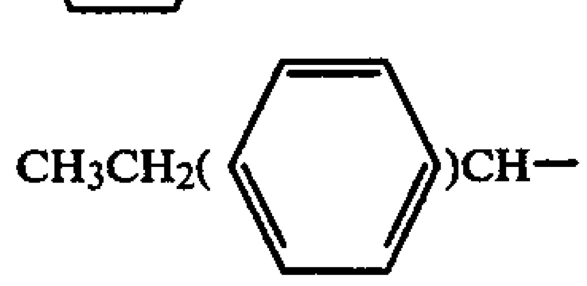
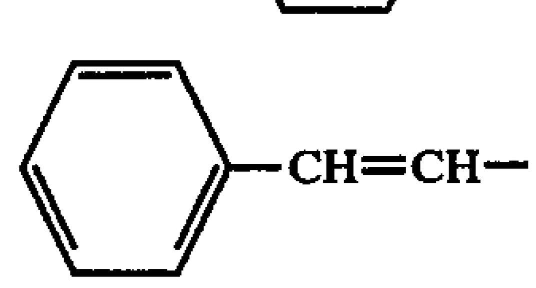
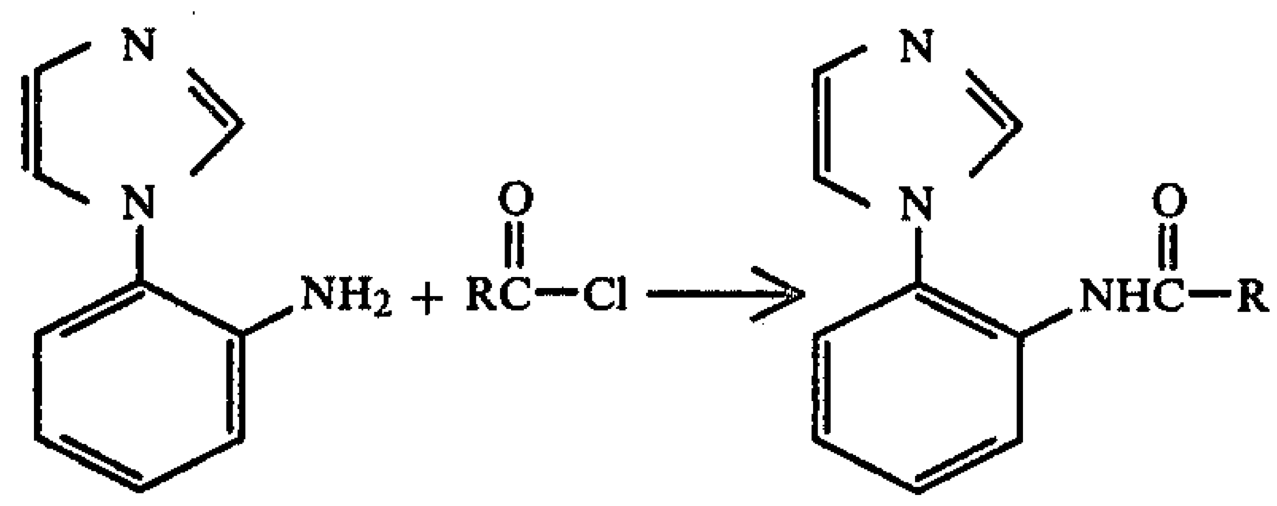
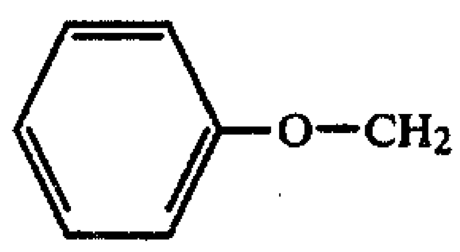
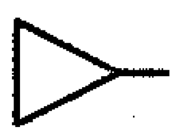
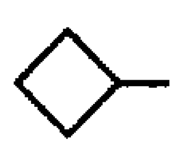
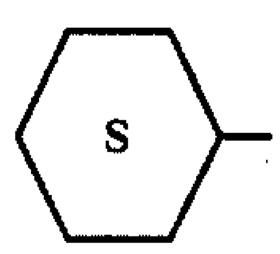
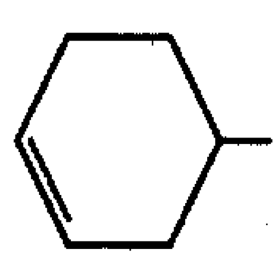
No.	R	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	Analysis Calc'd	Analysis Found
1	H—[a]	C	63.3	Water	200–204	C,64.16 H, 4.85 N,22.45	64.26 4.71 22.30
2	CH_3—	A	56.2	Ethanol	163–166	C,65.66 H, 5.51 N,20.88	65.69 5.52 20.84
3	CH_3CH_2—[b]	C	73.9	Water	144–146	C,66.96 H, 6.09 N,19.52	67.26 6.15 19.40
4	$CH_3(CH_2)_2$—	B	31.1	Toluene	108–110	C,68.10 H, 6.59 N,18.33	67.95 6.52 18.25
5	$CH_3(CH_2)_3$—	B	49.6	Toluene-hexane	123–125	C,69.11 H, 7.04 N,17.27	69.14 7.00 17.17
6	$CH_3(CH_2)_4$—	B	49.4	isopropyl ether-trichloroethylene	103–105	C,70.01 H, 7.44 N,16.33	70.31 7.45 16.26
7	$CH_3(CH_2)_5$—	A	55.3	isopropyl ether	96–98	C,70.82 H, 7.80 N,15.48	70.79 7.74 15.23
8	$CH_3(CH_2)_6$—	A	55.1	isopropyl ether	101–102	C,71.55 H, 8.12 N,14.72	71.67 8.05 14.65
9	$CH_3(CH_2)_7$—	A	45.6	isopropyl ether	93–95	C,72.21 H, 8.42 N,14.03	72.24 8.41 13.92
10	$CH_3(CH_2)_8$—	A	60.6	isopropyl ether-hexane	79–81	C,72.81 H, 8.68 N,13.41	73.38 8.85 13.02
11	$CH_3(CH_2)_{14}$—	B	58.1	isopropyl ether	94–96	C,75.52 H, 9.89 N,10.57	75.12 9.76 10.38
12	$CH_3(CH_2)_{16}$—	B	80.6	isopropyl ether	98–100	C,76.19 H,10.18 N, 9.87	76.57 10.28 9.79
13	$(CH_3)_3C$—[b]	C	48.8	benzene	102–104	C,69.11 H, 7.04 N,17.27	69.15 7.26 17.19
14	$(CH_3)_2CHCH_2$—	C	25.4	benzene	128–130	C,69.40 H, 6.66 N,17.34	69.60 7.00 17.40
15	$CH_3(CH_2)_3(CH_3CH_2)CH$—	B	32.8	benzene	125–127	C,71.55 H, 8.12 N,14.72	71.86 7.84 14.95
16	CH_2—CH—$(CH_2)_8$—	A	76.8	isopropyl ether-hexane	92–94	C,73.81 H, 8.36 N,12.91	74.26 8.50 12.30
17	$CH_3(CH_2)_3(CH_2$—CH=CH$)_2(CH_2)_7$—	C	3.6	c.	73.76	C,76.92 H, 9.32 N, 9.97	76.73 9.36 9.78
18		C	41.9	ethanol	145.147	C,73.63 H, 5.45 N,15.15	73.81 5.57 15.41
19		C	7.7	diethyl ether	205–207	C,74.73 H, 6.27 N,13.76	74.83 6.32 13.59
20		A	43.0	ethanol	161–164	C,74.72 H, 5.23 N,14.52	74.94 5.47 14.55

TABLE I-continued

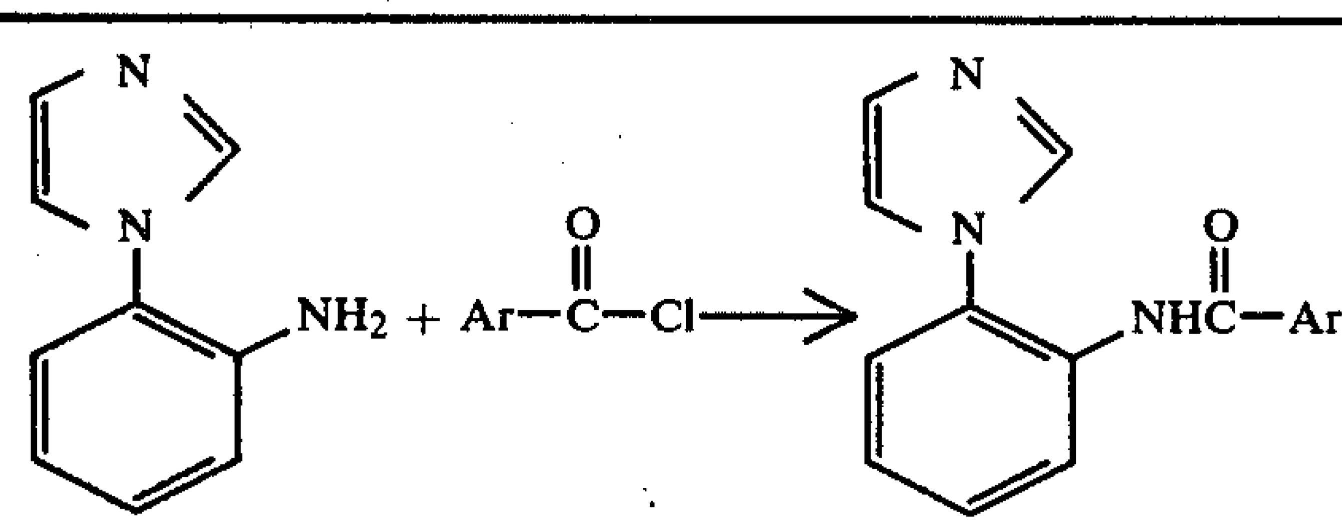


1-(2-alkanamidophenyl)imidazoles

No.	R	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	Analysis Calc'd	Analysis Found
21	CH_3OCH_2-	A	49.8	Toluene	146–147	C,62.33 H, 5.66 N,18.17	61.99 5.74 18.48
22		A	77.7	Toluene	136.5–138.5	C,69.61 H, 5.15 N,14.33	69.82 5.37 14.04
23		A	10.1	isopropanol	207–209	C,68.71 H, 5.76 N,18.49	68.67 5.85 18.67
24		A	55.6	Toluene	151–153	C,69.69 H, 6.27 N,17.41	69.44 6.21 17.55
25		A	67.3	Toluene	142.5–145	C,71.35 H, 7.11 N,15.60	70.88 6.92 15.59
26		A	21.6	ethanol	196–198.5	C,72.16 H, 6.06 N,15.78	71.87 6.33 15.40
27	CH_2Cl-	B	11.9	water	255(dec.)	C,56.06 H, 4.28 N,17.83	55.92 4.26 17.72
28	CH_3CHCl-	A	27.9	Toluene	143.5–145.5°	C,57.72 H, 4.85 H,16.83	57.54 4.92 17.16
29	$CHCl_2-$[b]	A	33.2	benzene	162–165	C,48.91 H, 3.36 N,15.56 Cl,26.25	48.94 3.24 15.42 26.17
30	CF_3-	A	22.0	ethanol	165–167	C,51.77 H, 3.16 N,16.47	51.58 3.20 16.53
32	$CH_3CH_2O\overset{O}{\overset{\Vert}{C}}-$	C	14.1	trichloro-ethylene	128–130	C,60.23 H, 5.05 N,16.21	60.21 5.10 16.16

Notes:
a. Prepared from acetic-formic anhydride according to R. J. Jones, J. Am. Chem. Soc., 71,644(1949). After removal by distillution of excess solvent, residue dissolved in water and neutralized with NaOH to provide crude product.
b. Prepared via the anhydride.
c. Could not be crystallized; purified by chromatography on alumina with ethyl acetate as elutant.

TABLE II



1-(2-Arylamidophenyl)imidazoles

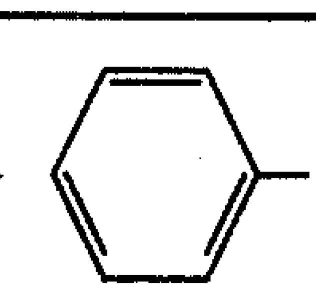
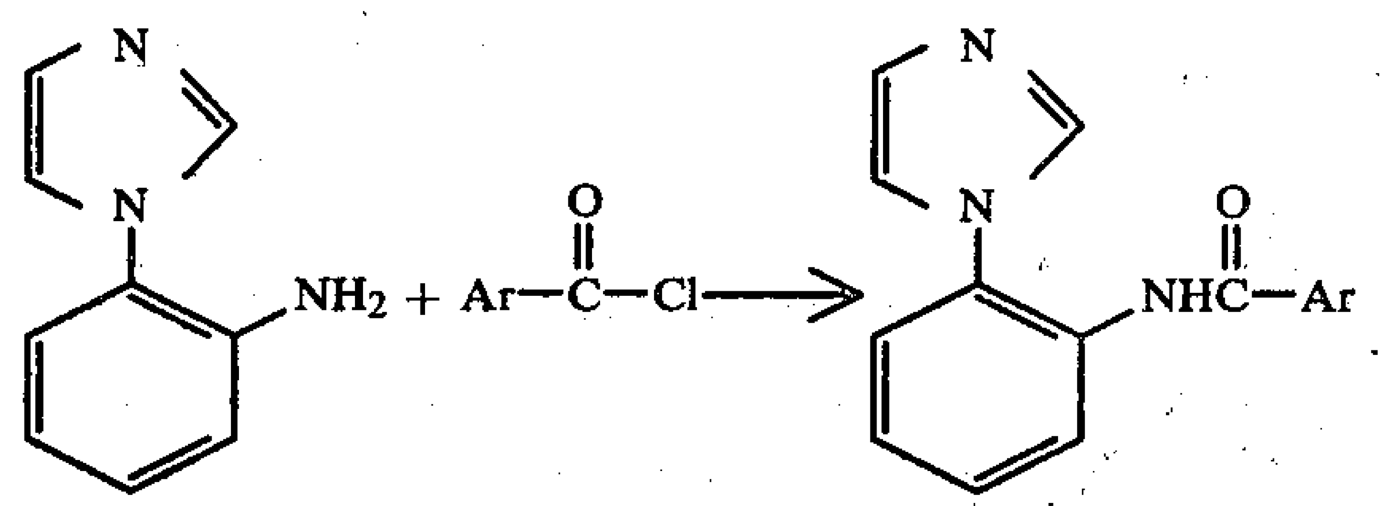
No.	Ar	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
34		A	44.9	dimethoxyethane	148–150	225(21,720)	C,72.99 H, 4.98 N,15.96	73.30 5.08 16.04

TABLE II-continued



1-(2-Arylamidophenyl)imidazoles

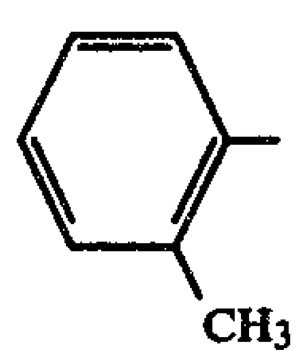
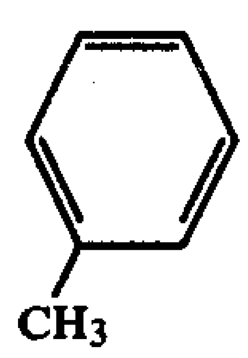
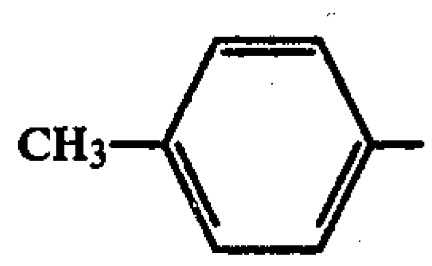
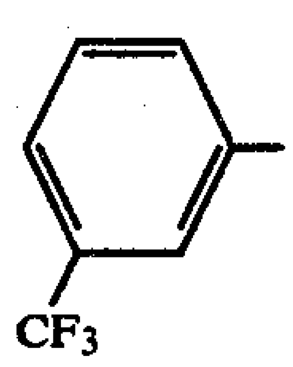
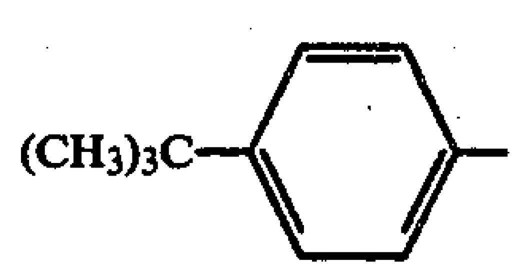
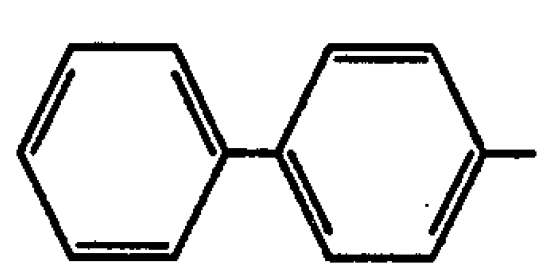
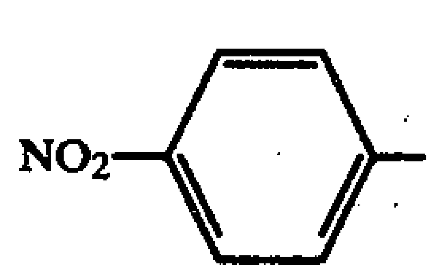
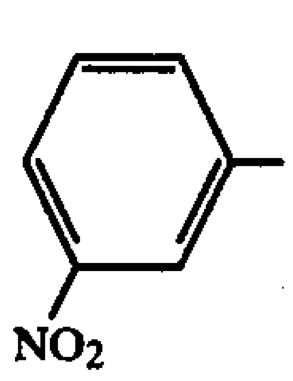
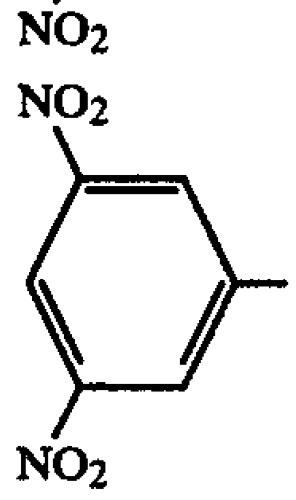
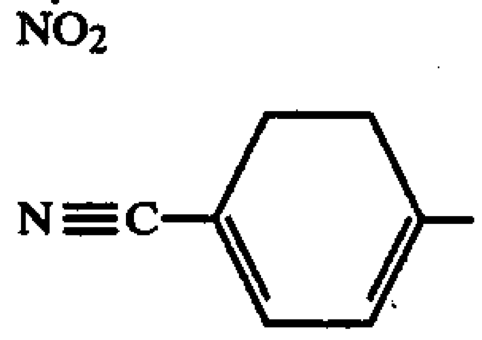
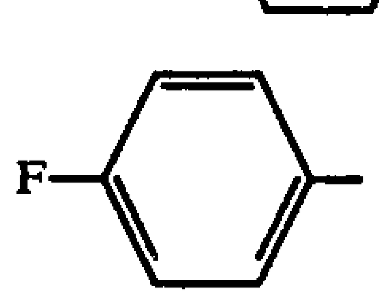
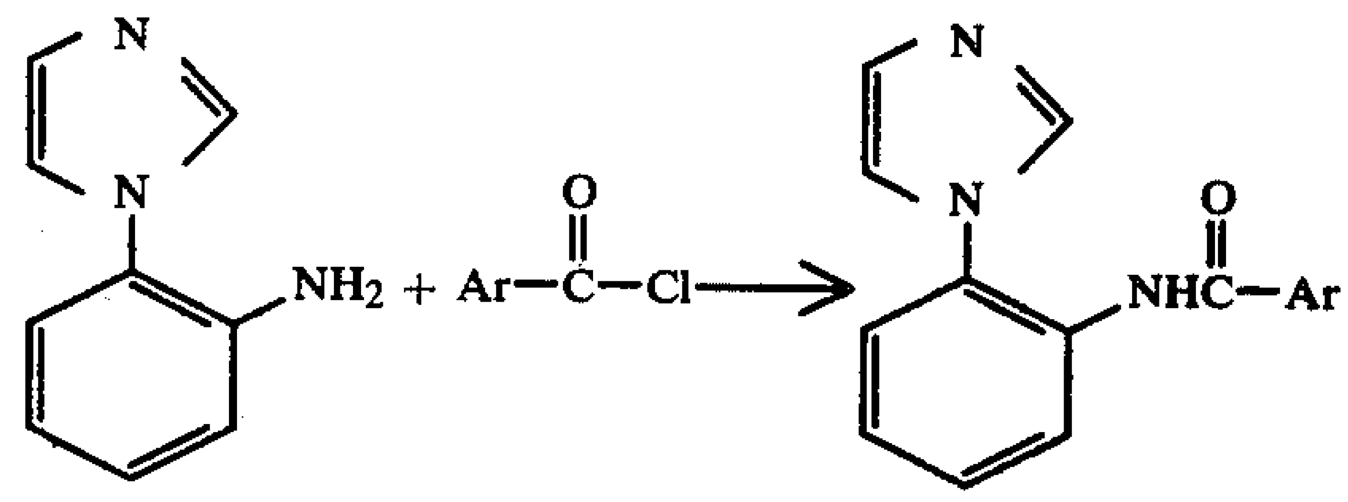
No.	Ar	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
35		A	58.7	ethanol	190–192.5	262(21,400)	C,73.63 H, 5.45 N,15.15	73.10 5.32 15.46
36		B	58.3	benzene	147–148.5	231,sh(18,200)	C,73.63 H, 5.45 N,15.15	73.63 5.24 15.36
37		B	57.4	benzene	143–146.5	236(23,400)	C,73.63 H, 5.45 N,15.15	73.28 5.29 15.27
38		A	53.0	benzene	151–153	c.	C,61.63 H, 3.65 N,12.68	60.97 3.62 12.34
39		B	79.3	ethyl acetate	136–138	239(20,400)	C,75.21 H, 6.63 N,13.27	75.06 6.45 13.31
40		A	45.5	isopropanol	198–200	276(28,100)	C,77.86 H, 5.05 N,12.38	77.46 4.76 12.09
41		A	73.5	dimethylformamide, ethanol	194–196	260(17,810)	C,62.33 H, 3.92 N,18.17	62.26 3.69 18.10
42		A	74.4	dimethylformamide, water	198–202.5	250(16,500)	C,62.33 H, 3.92 N,18.17	62.27 4.00 18.37
43		A	87.41	dimethylformamide, water	254–256	c.	C,54.40 H, 3.14 N,19.82	54.35 3.31 19.82
44		A	60.87	dimethylformamide, water	219–220.5	234(1,500)	C,70.82 H, 4.20 N,19.49	70.14 4.45 19.15
45		B	56.8	benzene	205–208	229(18,500)	C,68.32 H, 4.30 N,14.94	67.86 4.02 15.17

TABLE II-continued



1-(2-Arylamidophenyl)imidazoles

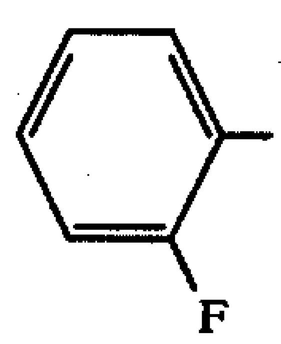
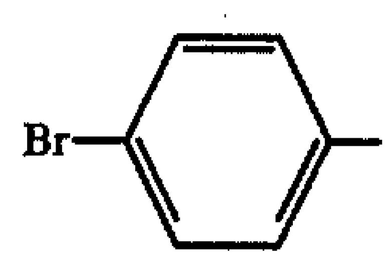
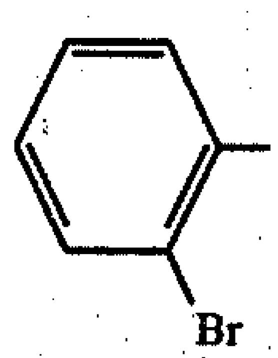
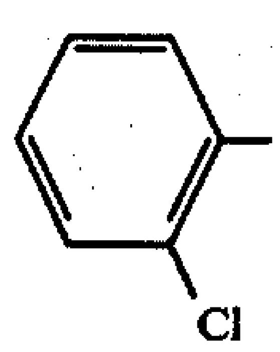
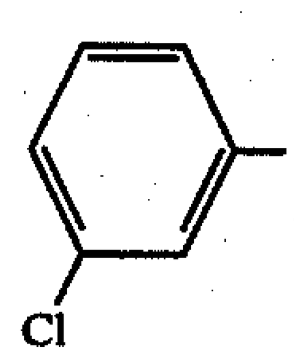
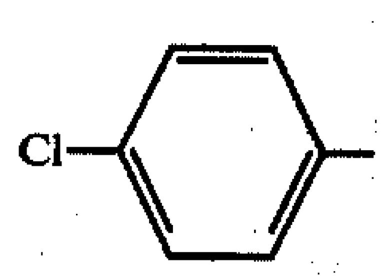
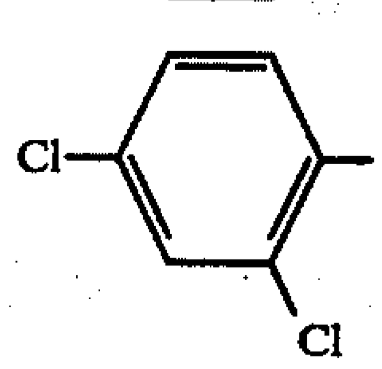
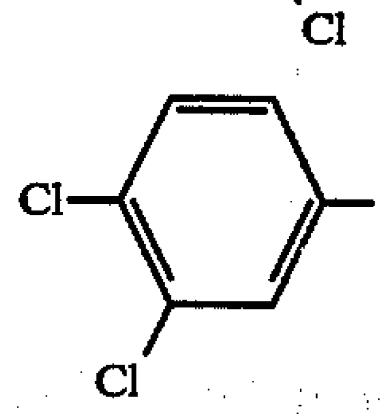
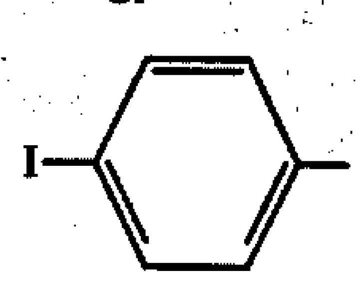
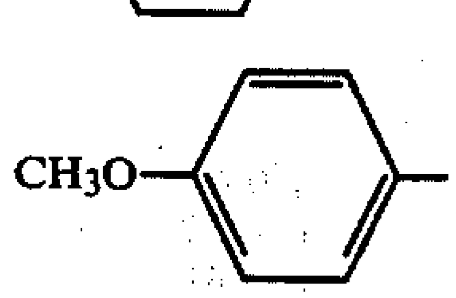
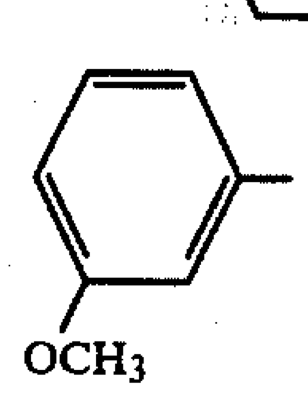
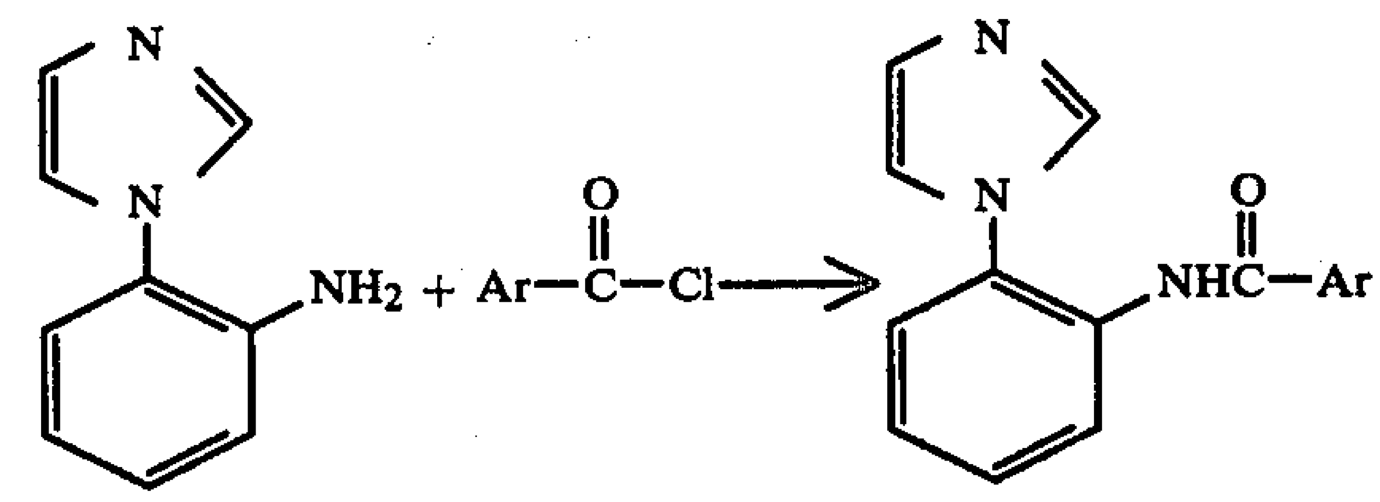
No.	Ar	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
46		A	53.2[a]	dimethylformamide, water	93–96	260(10,100)	C,66.20 H, 4.51 N,14.47	65.96 4.37 14.40
47		A	b.	dimethylformamide	189–190.5	240(22,100)	C,56.16 H, 3.53 N,12.28	56.03 3.58 12.51
48		A	40.1	dimethylformamide, water	199–201.5	258(20,100)	C,56.16 H, 3.54 N,12.28	55.84 3.58 12.48
49		A	38.7	dimethylformamide, ethanol	201–203	261(16,700)	C,64.54 H, 4.06 N,14.11	64.70 4.05 13.95
50		B	68.5	ethanol	144–146	c.	C,64.54 H, 4.06 N,14.11	64.82 3.92 14.59
51		A	59.7	ethanol	167–170	240(26,410)	C,64.54 H, 4.06 N,14.11	64.41 3.94 13.92
52		A	26.6	dimethylformamide, water	210–212	265(21,000)	C,57.85 H, 3.34 N,12.65	58.05 3.46 13.08
53		A	61.2	dimethylformamide, water	180.5–183	235(22,100)	C,57.85 H, 3.34 N,12.65	57.65 3.51 12.93
54		A	42.9	ethanol	186.5–189	255(28,480)	C,49.38 H, 3.11 N,10.80 I,32.61	49.22 3.15 10.85 32.89
55		B	58.6	isopropanol	146–151	263(20,400)	C,69.61 H, 5.15 N,14.33	69.01 5.14 14.36
56		B	83.2	dimethylformamide, water	171–173	281(5,100)	C,69.61 H, 5.15 N,14.33	69.27 5.02 14.28

TABLE II-continued



1-(2-Arylamidophenyl)imidazoles

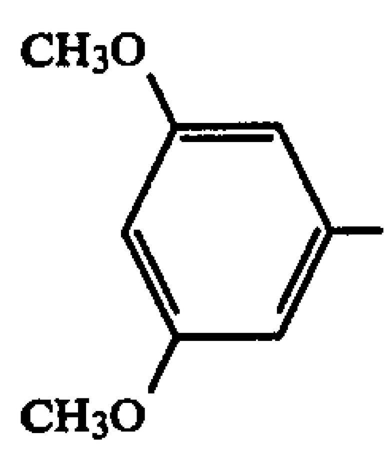
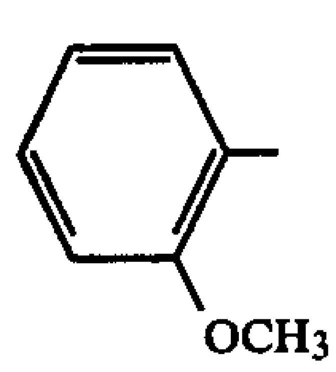
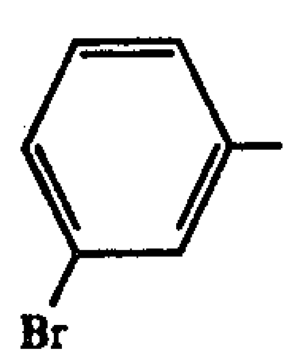
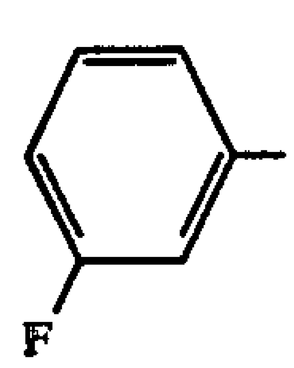
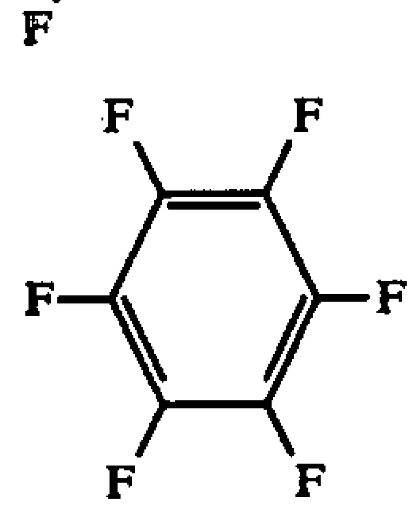
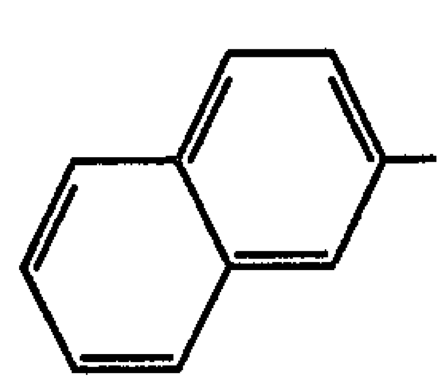
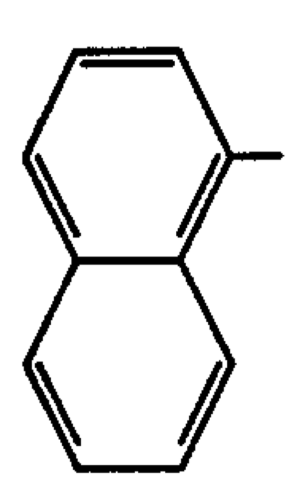
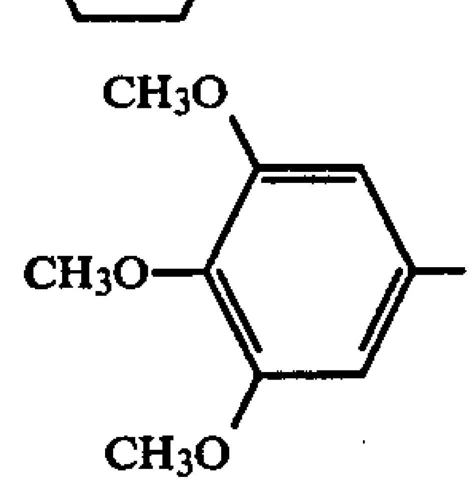
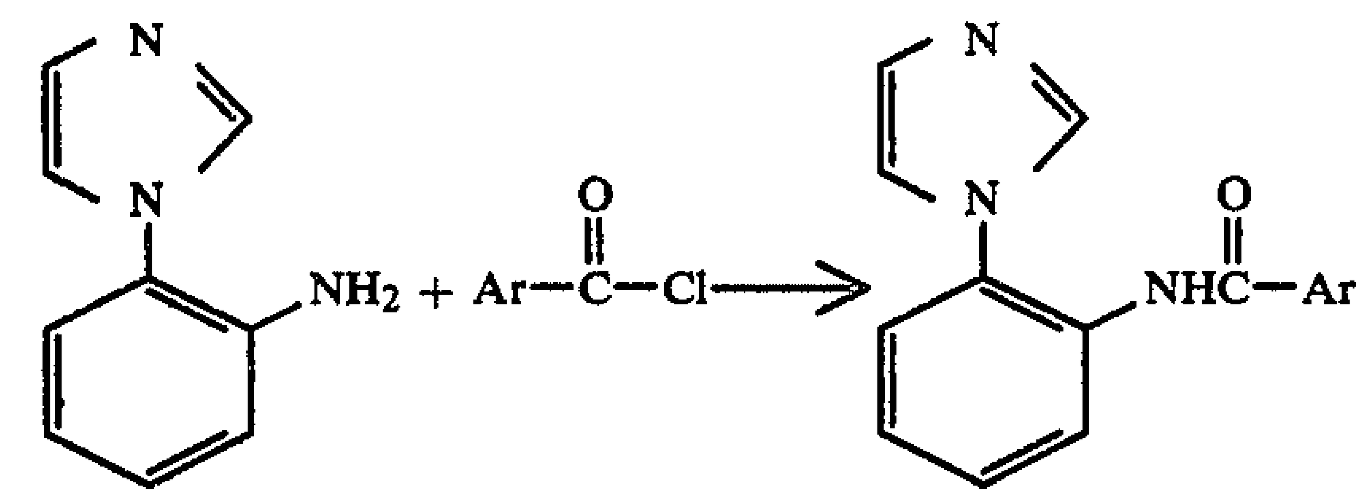
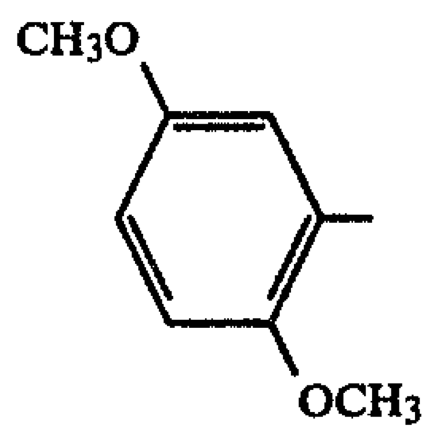
No.	Ar	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
57		B	61.2	benzene	130–132.5	244,sh(12,300)	C,66.86 H, 5.30 N,13.00	66.97 5.08 13.54
58		C	29.79	dimethylformamide, water	133.5–136.5	281(15,410)	C,69.61 H, 5.15 N,14.33	69.10 5.08 14.18
59		B	18.26	dimethylformamide, water	164.5–166.5	c.	C,56.16 H, 3.54 N,12.28	55.65 3.51 12.37
60		A	51.07	isopropanol	142.5–145.5	223(14,420)	C,68.32 H, 4.30 N,14.94	67.79 4.36 14.58
61		B	15.68	isopropanol-ethanol	203.5–205	258(18,840)	C,54.40 H, 2.28 N,11.90	53.78 2.30 12.16
62		A	46.9	isopropanol	165.5–167.5	237(53,900)	C,76.66 H, 4.83 N,13.41	76.29 4.84 13.27
63		A	36.78	isopropanol-dimethylformamide	175–177	289(6,940)	C,76.66 H, 4.82 N,13.41	76.68 4.75 12.01
190		B	38.80	benzene	156–157.5	268(13,800)	C,64.58 H, 5.42 N,11.89	64.58 5.39 12.02

TABLE II-continued



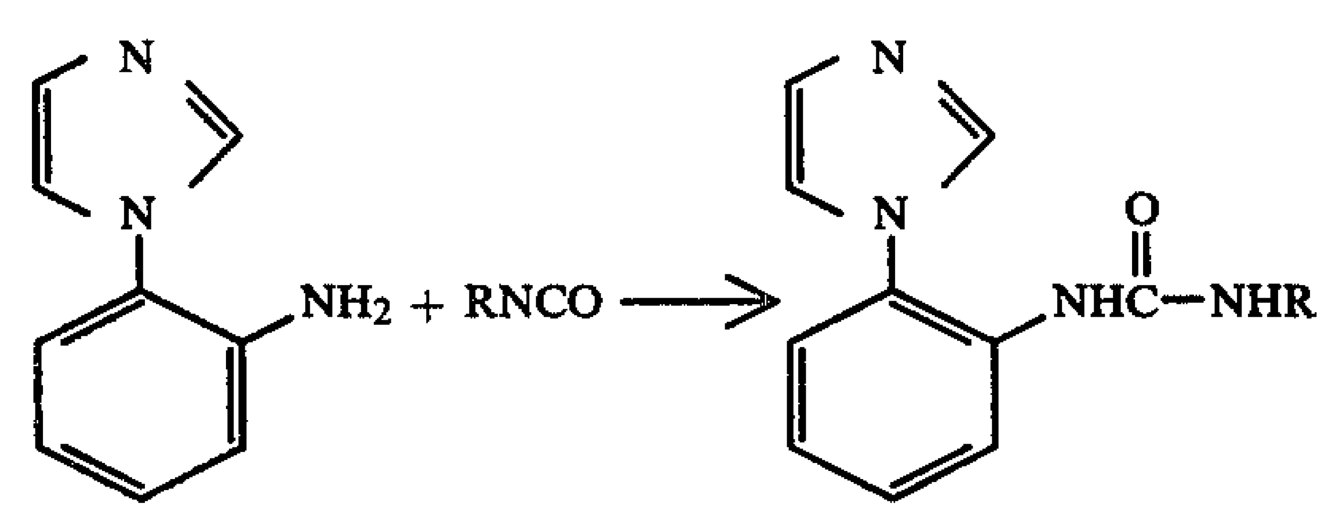
1-(2-Arylamidophenyl)imidazoles

No.	Ar	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
217		A	45.8	ethanol	134–136.5	273(14,900)	C,66.86 H, 5.30 N,13.00	66.88 5.37 12.68

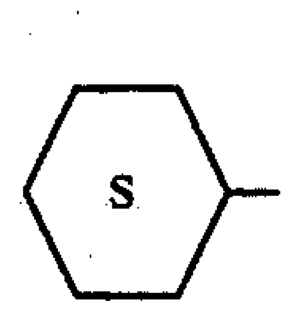
Notes:
a. isolated as hemihydrate.
b. partial loss prevented yield determination.
c. Compound absorbed too low for significant U.V.

Alkyl-2-(1-imidazolyl)phenylureylenes (Table III) were prepared by the reaction of equimolar amounts of the aminophenylimidazole and the appropriate isocyanate in toluene solution at steam bath temperatures during two or three hours. Upon cooling, the crude product was collected by filtration and treated by one of the following methods: (A) direct crystallization from the appropriate solvent or (B) dissolved in hot dimethylformamide and precipitated with water followed by crystallization.

TABLE III

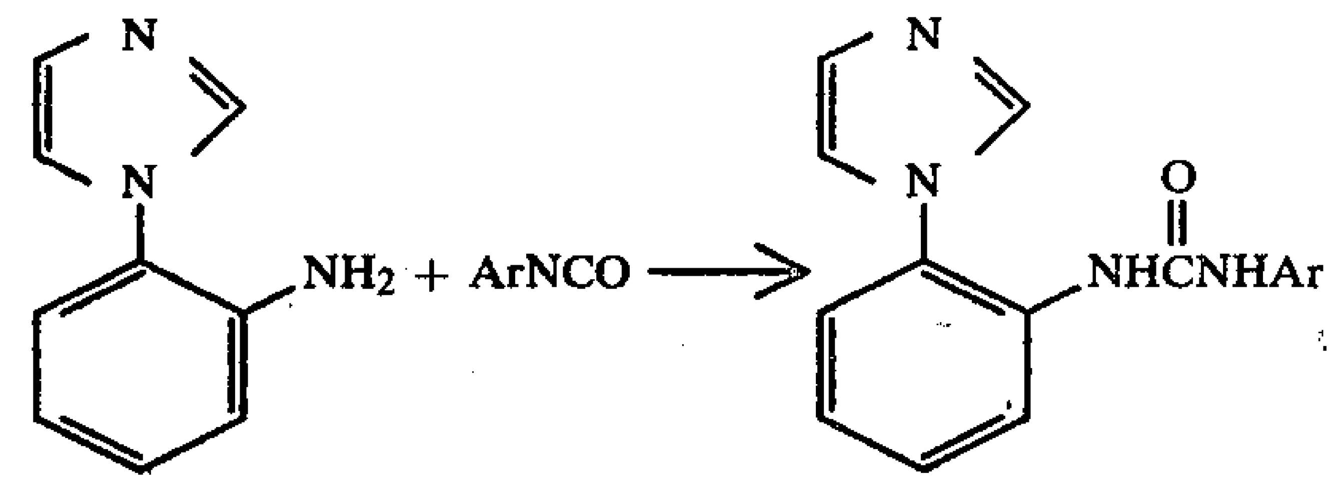


Alkyl-2-(1-imidazolyl)phenylureylenes

No.	R	Isolation Method	% Yield	Crystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
64	CH_3—	A	41.6	ethanol	194–196	240(15,500)	C,61.60 H, 5.59 N,25.91	61.22 5.48 26.11
65	CH_3CH_2—	B	27.3	trichloroethylene	173–175	278(1,200) 242(12,700)	C,62.59 H, 6.13 N,24.33	62.21 6.04 24.32
66	$CH_3CH_2CH_2$—	B	49.3	trichloroethylene	139–141	279(1,200) 240(12,800)	C,63.92 H, 6.60 N,22.93	63.75 6.56 23.00
67	$CH_3CH_2CH_2CH_2$—	B	35.6	isopropanol	115–116.5	278(1,400) 241(15,000)	C,65.09 H, 7.02 N,21.69	64.84 7.00 21.78
68		A	50.64	dimethylformamide, water	164–166	241(12,200)	C,67.58 H, 7.09 N,19.70	67.60 7.08 19.44

Aryl-2-(1-imidazolyl)phenylureylenes (Table IV) were prepared by reacting equimolar amounts of the aminophenylimidazole and the appropriate arylisocyanate in dry toluene during three hours at steam bath temperatures. The reaction mixture was cooled and the crude product was separated by filtration, and washed with ether and crystallized from the indicated solvent.

TABLE IV



Aryl-2-(1-imidazolyl)phenylureylenes

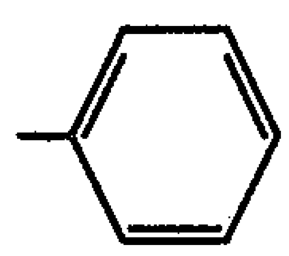
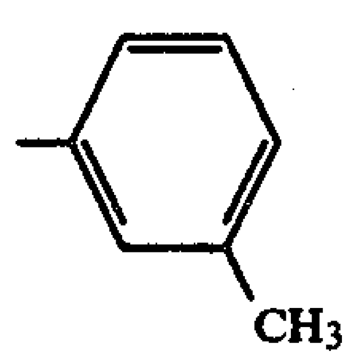
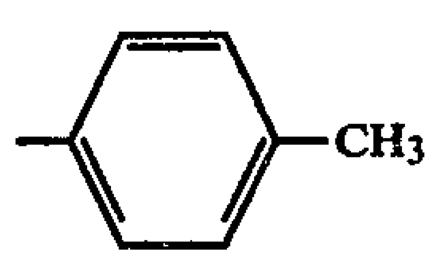
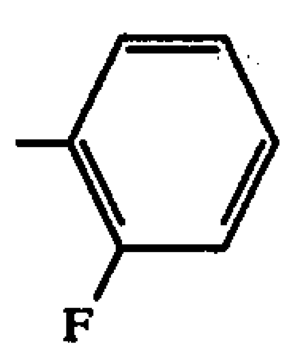
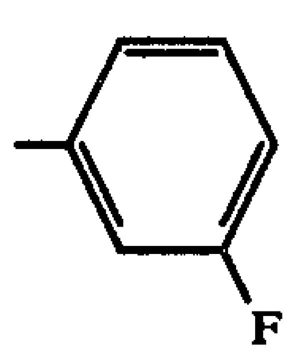
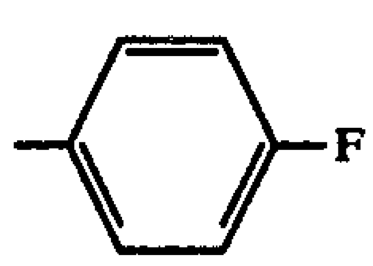
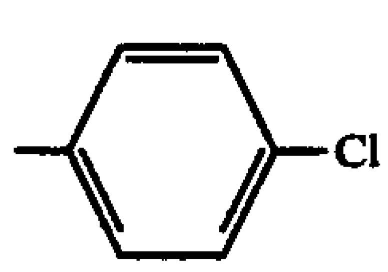
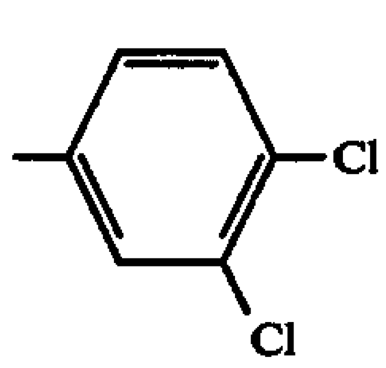
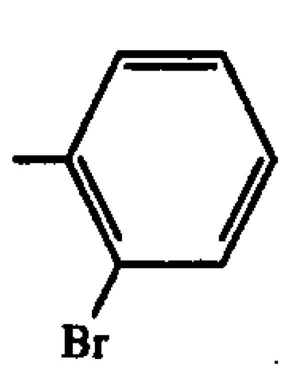
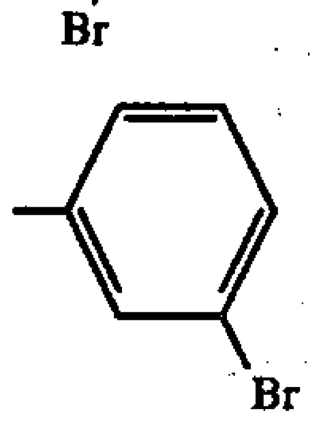
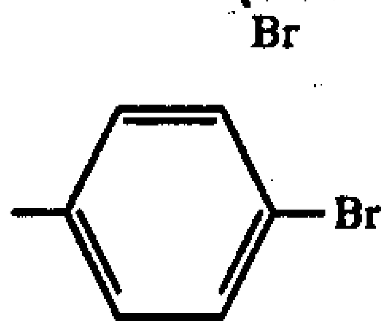
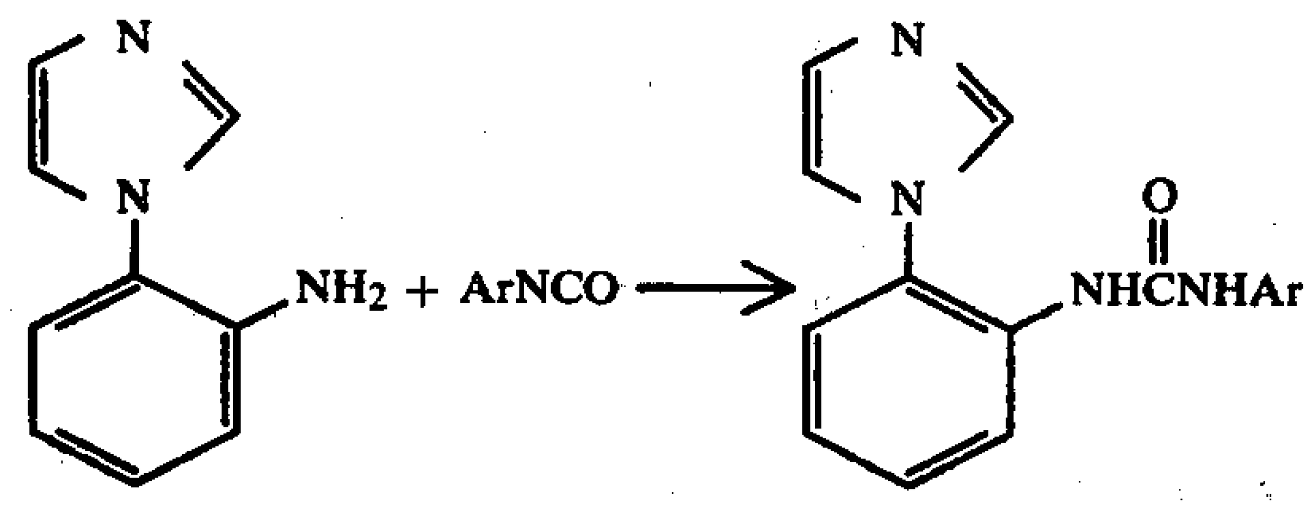
No.	Ar	% Yield	Recrystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
69		64.6	ethanol	201–203	256(27,640)	C,69.05 H, 5.07 N,20.13	69.13 5.15 20.16
70		76.9	dimethylformamide-water	203.5–207.5	258(23,400)	C,69.84 H, 5.52 N,19.17	69.85 5.47 19.28
71		76.9	ethanol	182–183.5	256(25,800)	C,69.84 H, 5.52 N,19.17	69.97 5.35 19.12
72		78.8	dimethylformamide-water	202.5–203.5	251(25,500)	C,64.86 H, 4.42 N,18.91	64.77 4.47 19.16
73		61.9	dimethylformamide-water	201.5–202	253(26,000)	C,64.86 H, 4.42 N,18.97	64.47 4.40 19.24
74		65.8	dimethylformamide-water	220–222	251(23,100)	C,64.86 H, 4.42 N,18.97	64.56 4.41 19.14
75		76.7	dimethylformamide-water	204–206	258(30,900)	C,61.45 H, 4.19 N,17.91	61.57 4.12 18.26
76		58.1	dimethylformamide-water	244–245.5	260(32,900)	C,55.35 H, 3.48 N,16.14	54.93 3.47 16.25
77		70.0	dimethylformamide-water	180.5–182.5	252(23,000)	C,53.80 H, 3.76 N,15.68	53.88 3.78 15.66
78		75.2	dimethylformamide-water	218–219.5	258(28,600)	C,53.80 H, 3.67 N,15.68	53.71 3.66 15.35
79		53.1	methanol	227–230.5	260(27,700)	C,53.80 H, 3.67 N,15.68	52.08 3.56 15.12

TABLE IV-continued



Aryl-2-(1-imidazolyl)phenylureylenes

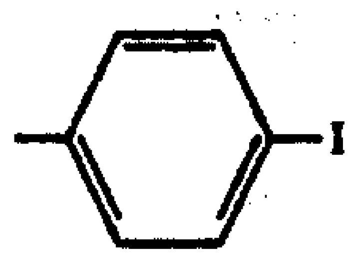
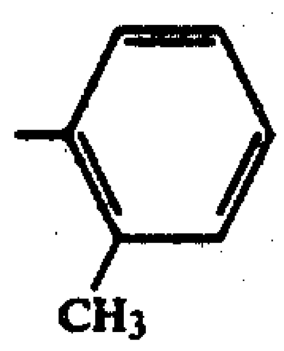
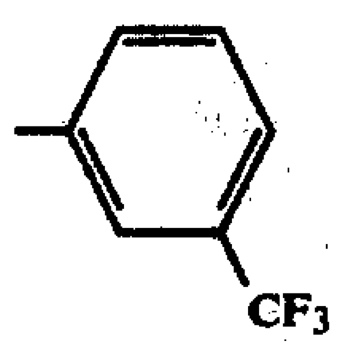
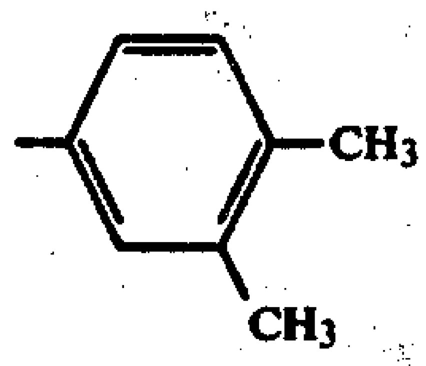
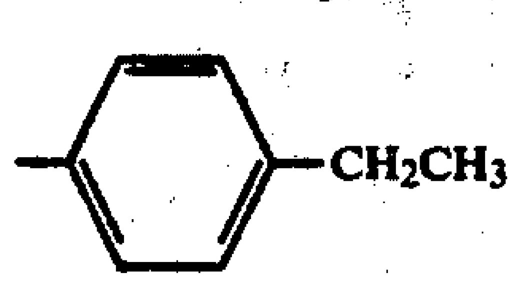
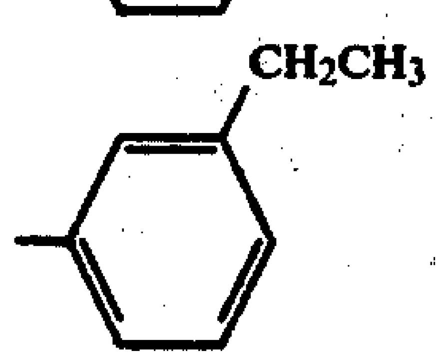
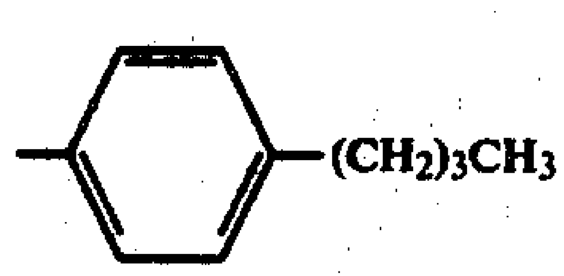
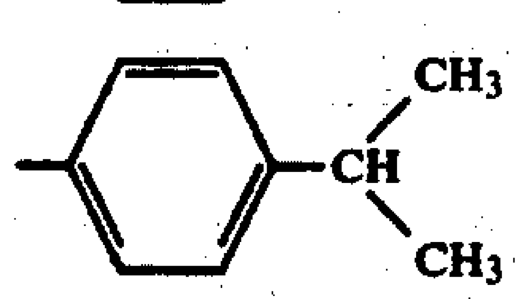
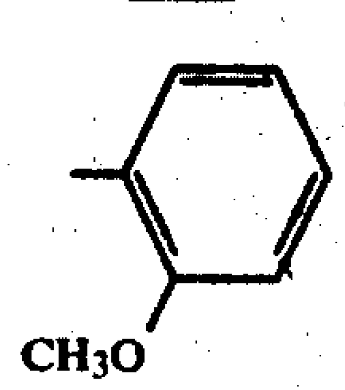
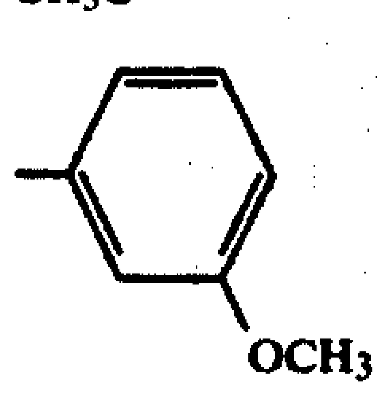
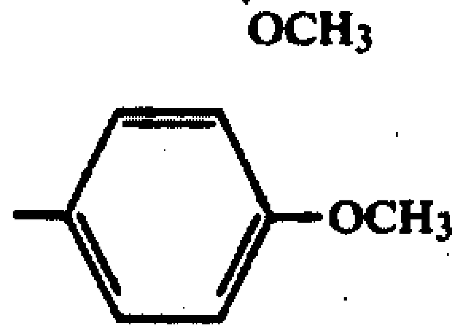
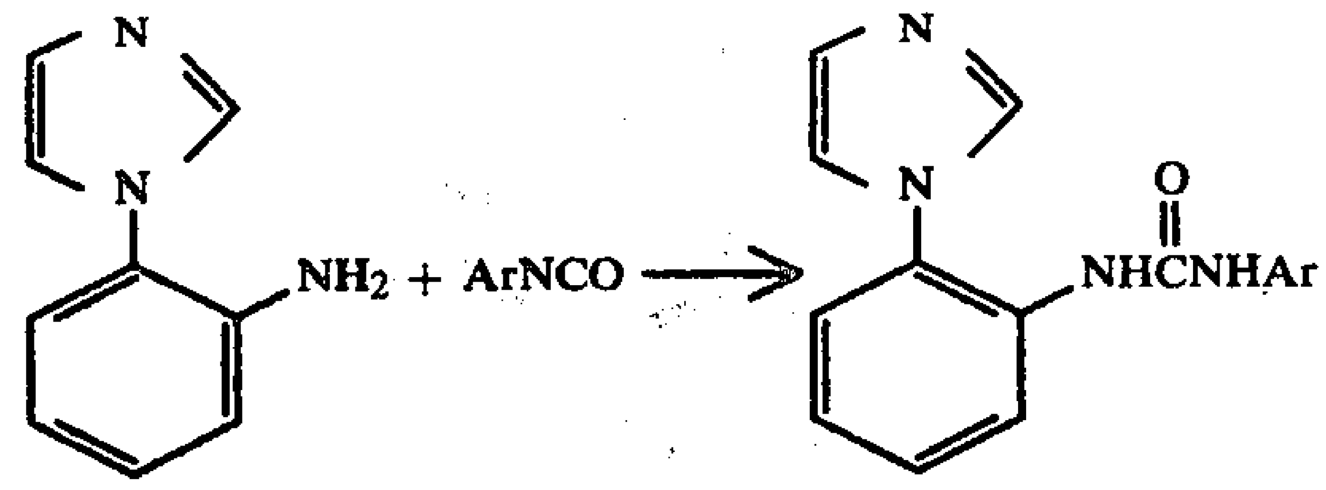
No.	Ar	% Yield	Recrystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
80		83.2	dimethylformamide-water	201–202	253(26,000)	C,64.86 H, 4.42 N,18.97	64.47 4.40 19.24
81		57.79	dimethylformamide-water	167–170	250(20,710)	C,69.84 H, 5.52 N,19.17	70.10 5.57 18.60
82		77.4	dimethylformamide-water	216.5–218.5	256(31,010)	C,58.96 H, 3.78 N,16.18	58.86 3.81 15.79
83		78.9	dimethylformamide-water	212–215	260(27,580)	C,70.57 H, 5.92 N,18.29	70.30 5.83 18.00
84		76.6	dimethylformamide-water	185–188	258(29,590)	C,70.57 H, 5.92 N,18.29	70.30 5.96 18.00
85		76.2	dimethylformamide-water	163.5–166	258(28,770)	C,70.57 H, 5.92 N,18.29	70.52 5.81 17.94
86		67.8	dimethylformamide-water	169–172	257(29,920)	C,71.83 H, 6.63 N,16.75	71.61 6.56 16.24
87		80.6	dimethylformamide-water	206–209	282(27,620)	C,71.23 H, 6.29 N,17.49	71.12 6.12 17.24
88		69.0	dimethylformamide-water	204.5–206	285(10,630)	C,66.22 H, 5.23 N,18.17	65.96 5.15 18.15
89		84.0	dimethylformamide-water	188	252(25,510)	C,66.22 H, 5.23 N,18.17	65.83 5.13 18.02
90		81.9	dimethylformamide-water	200–202	260(24,560)	C,66.22 H, 5.23 N,18.17	65.61 5.14 17.98

TABLE IV-continued



Aryl-2-(1-imidazolyl)phenylureylenes

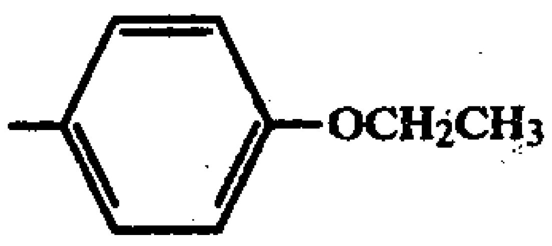
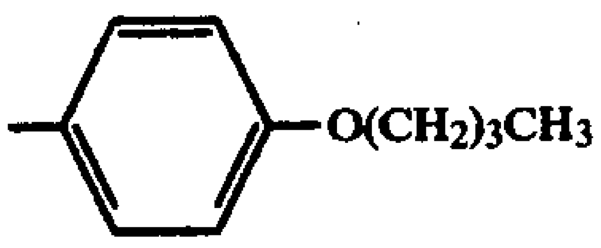
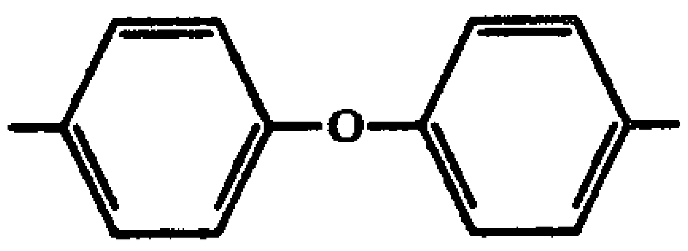
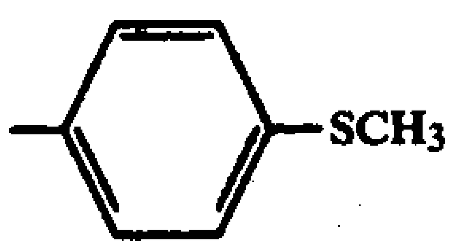
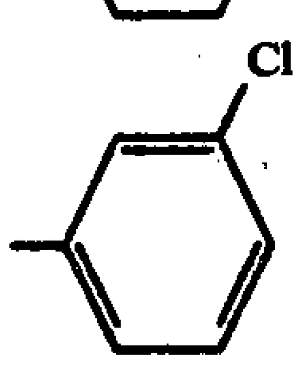
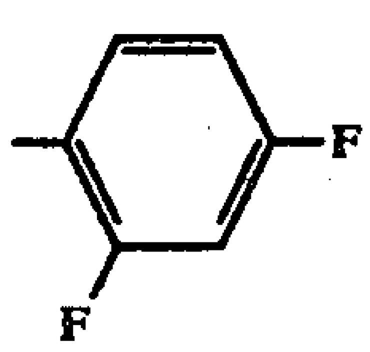
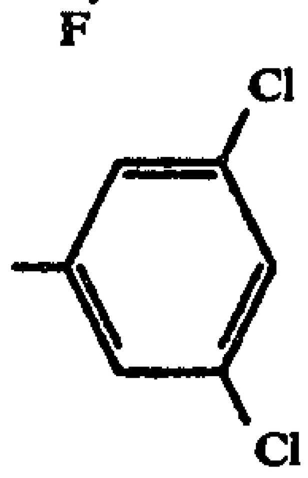
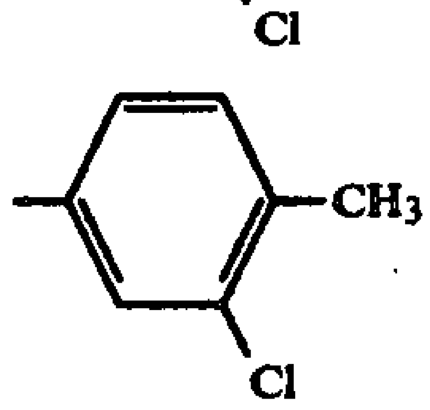
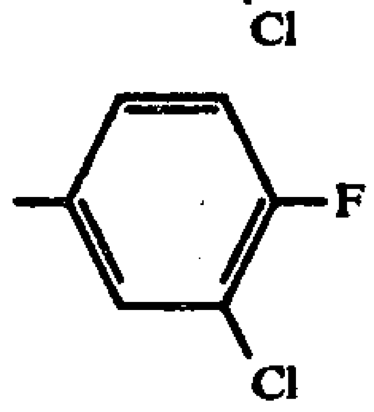
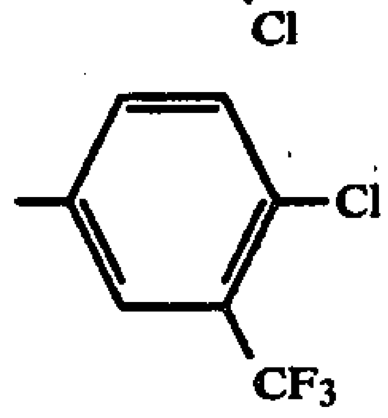
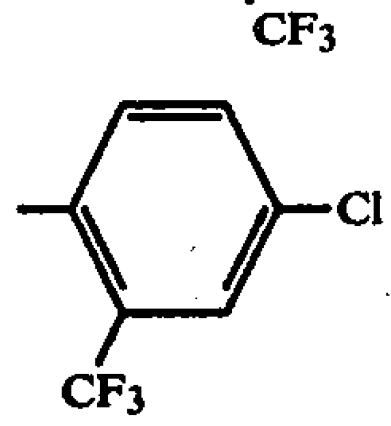
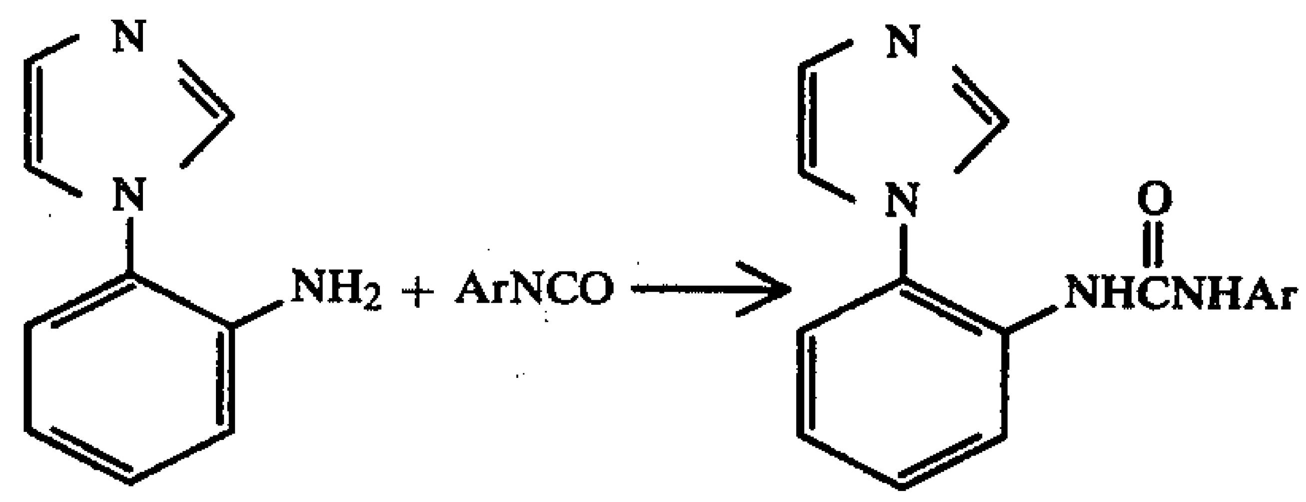
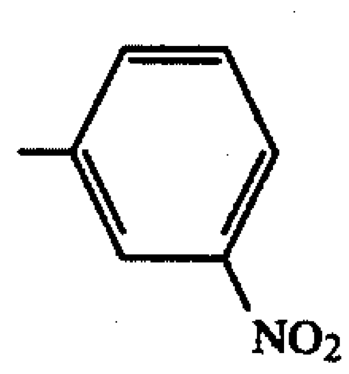
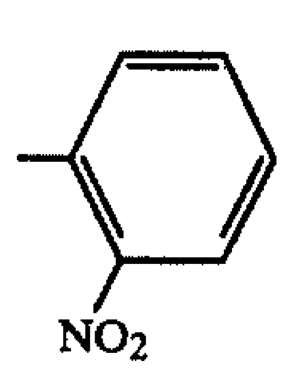
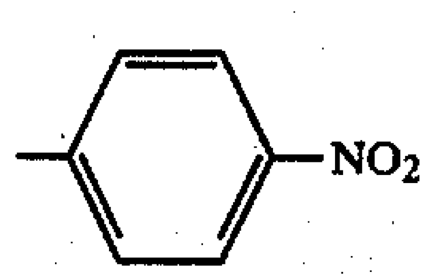
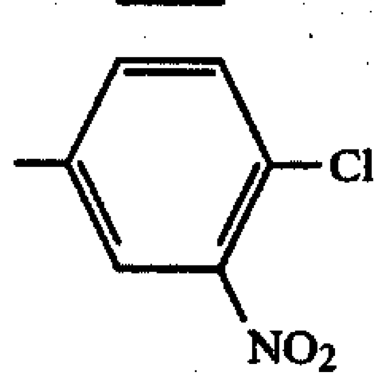
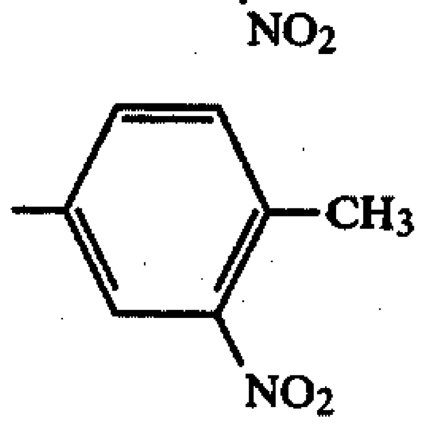
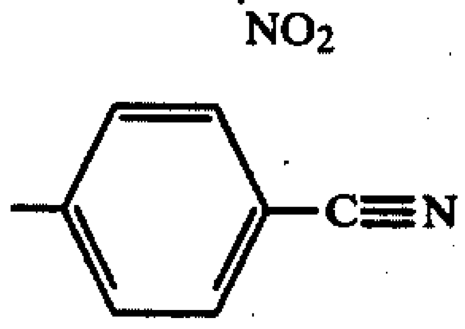
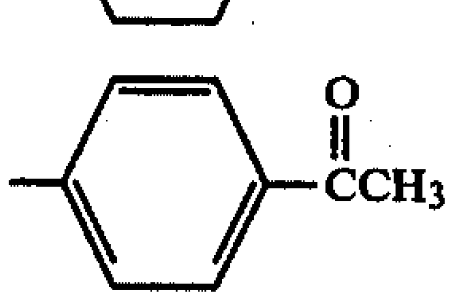
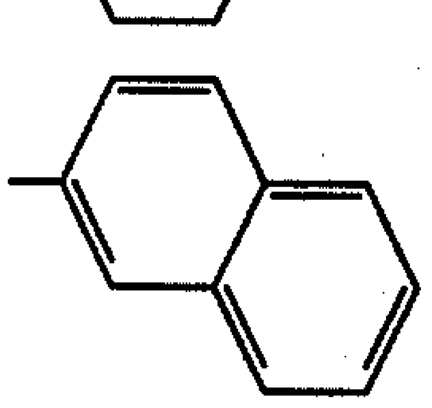
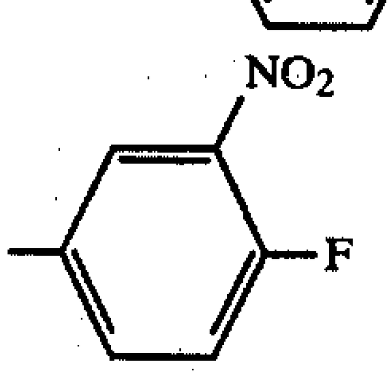
No.	Ar	% Yield	Recrystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
91		80.9	dimethylformamide-water	190.5–193	259(27,180)	C,67.07 H, 5.63 N,17.38	66.80 5.62 17.16
92		79.5	dimethylformamide-water	178–179.5	258(26,490)	C,68.55 H, 6.33 N,15.99	68.68 6.34 15.62
93		64.1	dimethylformamide-water	202.5–205	259(35,850)	C,71.34 H, 4.90 N,15.13	71.14 4.93 14.78
94		75.1	dimethylformamide-water	189–191	278(32,130)	C,62.94 H, 4.97 N,17.27	62.84 4.86 17.22
95		62.3	dimethylformamide-water	211.5–214.5	259(30,210)	C,61.45 H, 4.19 N,17.91	60.94 4.02 17.79
96		75.9	dimethylformamide-water	198–210	252(25,230)	C,61.44 H, 3.85 N,17.83	61.33 3.92 17.98
97		64.8	dimethylformamide-water	232.5–234	258(32,380)	C,55.35 H, 3.48 N,16.14	55.60 3.50 16.00
98		70.7	dimethylformamide-water	237.5–239	258(31,300)	C,62.48 H, 4.63 N,17.15	62.79 4.70 17.30
99		70.0	dimethylformamide-water	229–232	256(25,630)	C,58.10 H, 3.66 N,16.94	57.84 3.56 16.90
100		57.6	dimethylformamide-water	239.5–242.2	261(37,430)	C,53.63 H, 3.18 N,14.71	53.89 3.05 14.41
101		50.7	dimethylformamide-water	190–192	255(26,350)	C,53.63 H, 3.18 N,14.71	53.70 2.97 14.90

TABLE IV-continued

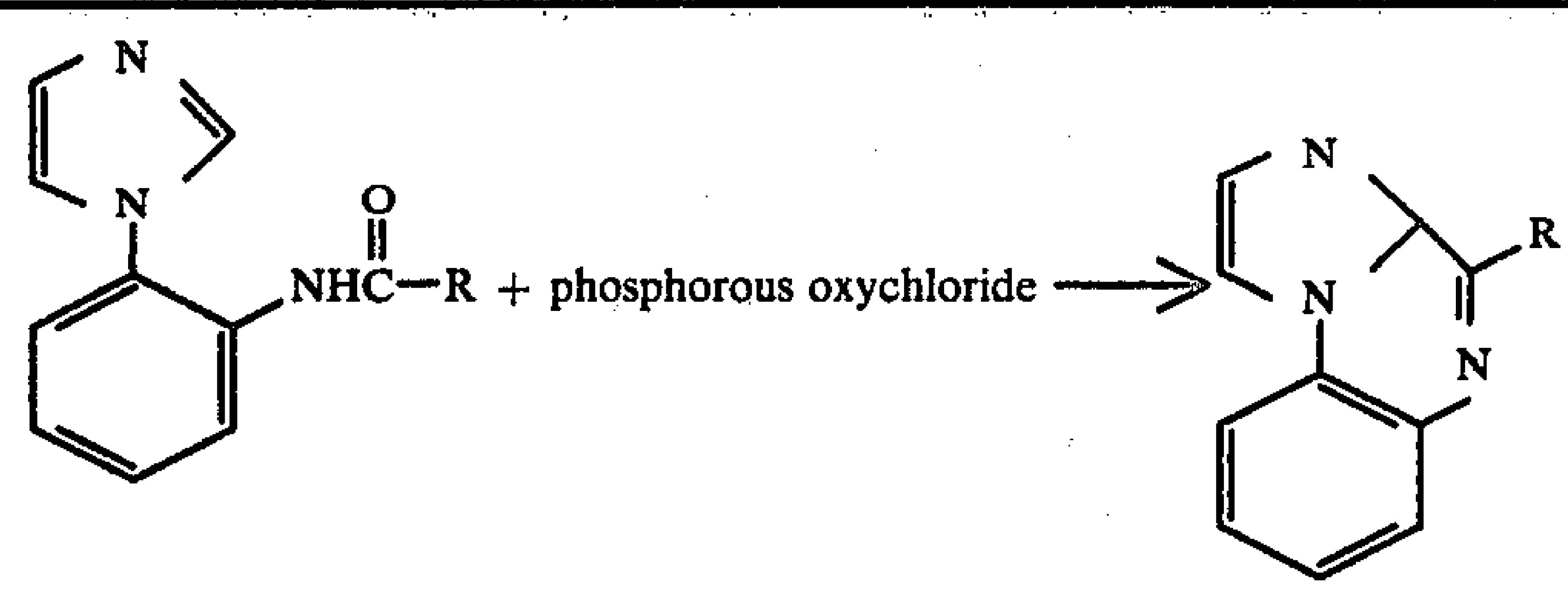


Aryl-2-(1-imidazolyl)phenylureylenes

No.	Ar	% Yield	Recrystallization Solvent	m.p., °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
102		42.7	dimethylformamide-water	202-205	375(4,200) 253(32,970)	C,59.44 H, 4.05 N,21.66	59.40 4.10 21.44
103		44.2	dimethylformamide-water	237.5-239.5	342(1,800) 264(46,530)	C,59.44 H, 4.05 N,21.66	59.16 4.10 21.31
104		52.3	dimethylformamide-water	>257(Dec.)	330(20,010)	C,59.44 H, 4.05 N,21.66	59.01 3.97 21.07
105		35.4	dimethylformamide-water	256.5-258	257(33,080)	C,53.72 H, 3.38 N,19.57	53.72 3.31 19.63
106		57.1	dimethylformamide-water	254-256 (Dec.)	256(36,930)	C,60.53 H, 4.48 N,20.76	60.26 4.34 20.68
107		47.3	dimethylformamide-water	244	290(57,510)	C,67.32 H, 4.32 N,23.09	67.88 4.13 21.37
108		33.8	dimethylformamide-water	227.5-229.5	297(32,710)	C,67.48 H, 5.03 N,17.49	67.49 5.05 17.07
191		35.2	dimethylformamide-water	233-236	284(16,710)	C,73.15 H, 4.91 N,17.06	72.70 4.97 16.63
192		25.2	dimethylformamide-methanol-water	231-232	252(32,920)	C,56.31 H, 3.55 N,20.52	54.13 3.50 20.21

4-Alkylimidazo[1,2-a]quinoxalines (Table V) were prepared by refluxing the appropriate amide (Table I, compounds 1-33) with phosphorous oxychloride in excess pyridine during one hour. The reaction mixture was stirred into water and sufficient azeotrope removed to form a viscous residue which was dissolved in chloroform, dried over $MgSO_4$, and chromatographed through an alumina column. The chloroform was evaporated and the product crystallized from the indicated solvent.

TABLE V



4-alkylimidazo[1,2-a] quinoxalines

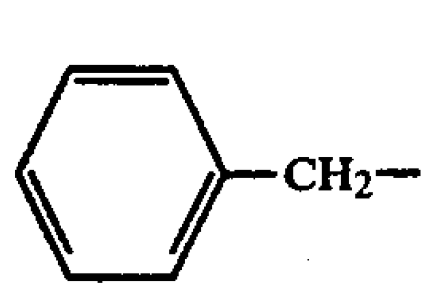
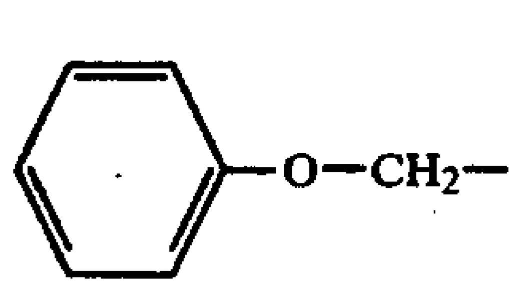
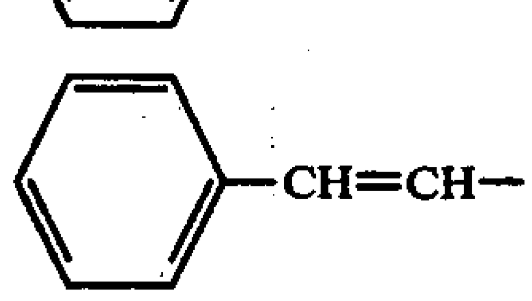
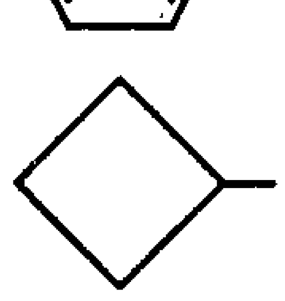
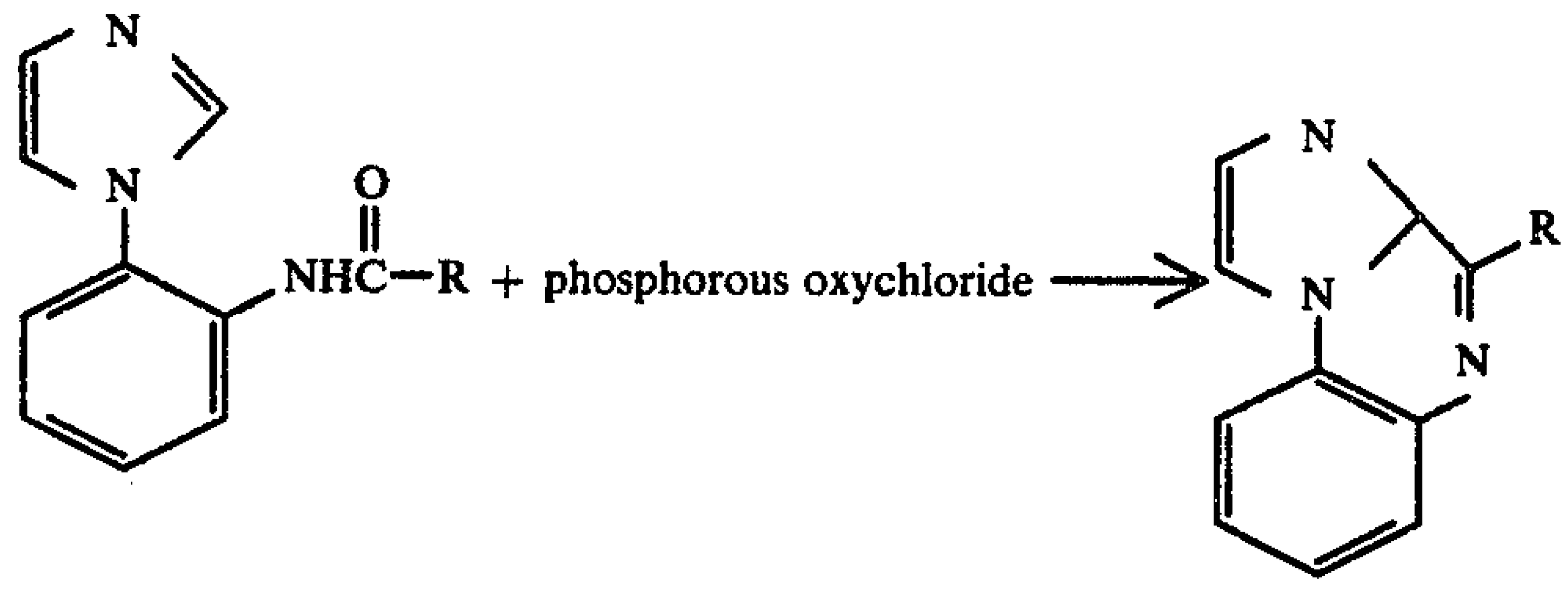
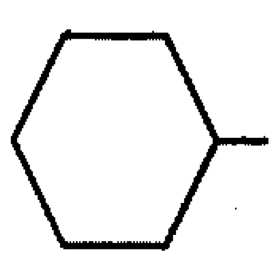
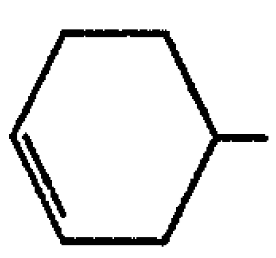
No.	R	% Yield	Recrystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
109	H— a.	63.3	sublimed	120	316(10,900)		
110	CH_3—	13.3	isopropyl ether	134–135	312(11,200)	C,72.11 H, 4.95 N,22.93	72.18 4.89 23.01
111	CH_3CH_2—	37.6	hexane	114–115	311(10,500)	C,73.07 H, 5.62 N,21.30	72.85 5.83 21.29
112	$CH_3CH_2CH_2$—	14.3	hexane	110–111	314(10,900)	C,73.91 H, 6.20 N,19.89	73.99 6.13 19.94
113	$CH_3(CH_2)_3$—	17.6	hexane	92–93	324(8,000)	C,74.64 H, 6.70 N,18.65	74.34 6.74 18.48
114	$CH_3(CH_2)_4$—	29.2	b.	63–65	314(11,300)	C,75.28 H, 7.16 N,17.56	75.13 7.39 17.43
115	$CH_3(CH_2)_5$—	10.7	b.	43–45	313(10,800)	C,75.86 H, 7.56 N,16.59	76.03 7.63 16.40
116	$CH_3(CH_2)_6$—	8.0	c.	54–57	313(9,400)	C,76.37 H, 7.92 N,15.72	75.84 7.77 16.43
117	$CH_3(CH_2)_7$—	26.3	isopropyl ether	65–66	311(11,600)	C,76.83 H, 8.24 N,14.93	76.97 8.20 14.89
118	$CH_3(CH_2)_8$—	9.5	ethyl ether-hexane	55–57	307(12,500)	C,77.25 H, 8.53 N,14.22	77.04 8.36 14.52
119	$CH_3(CH_2)_{14}$—	24.3	isopropyl ether	73–75	313(11,300)	C,79.11 H, 9.82 N,11.07	79.03 10.02 10.88
120	$CH_3(CH_2)_{16}$—	13.7	isopropyl ether-	79–81	311(11,300)	C,79.11 H,10.14 N,10.31	79.54 10.12 10.34
121	$(CH_3)_2CHCH_2$—	12.6	hexanes	52–55	314(11,700)	C,74.64 H, 6.71 N,18.65	74.92 6.81 18.74
122	CF_3—	50.7	isopropyl ether-chloroform	184–187	328(10,800)	C,55.70 H, 2.55 N,17.72	55.94 2.49 17.64
123	CH_2=$CH(CH_2)_8$—	9.8	hexanes	40–42	309(13,100)	C,78.14 H, 8.20 N,13.67	77.92 7.98 13.96
124		16.7	ethanol	140.5–142	312(13,100)	C,78.74 H, 5.05 N,16.20	78.59 5.20 16.10
125	CH_3OCH_2—	3.1	toluene-hexane	96.5–97.5	312(10,600)	C,67.59 H, 5.20 N,19.71	67.04 5.17 19.93
126		14.5	ethanol	146.5–148.5	314(10,400)	C,74.17 H, 4.76 N,15.26	74.28 4.61 15.09
127		37.2	benzene	164–167	286(10,500)	C,79.68 H, 4.83 N,15.49	80.38 4.91 15.12
128		17.9	hexane	106.5–107.5	310(11,500)	C,75.31 H, 5.87 N,18.82	75.32 5.84 18.75

TABLE V-continued



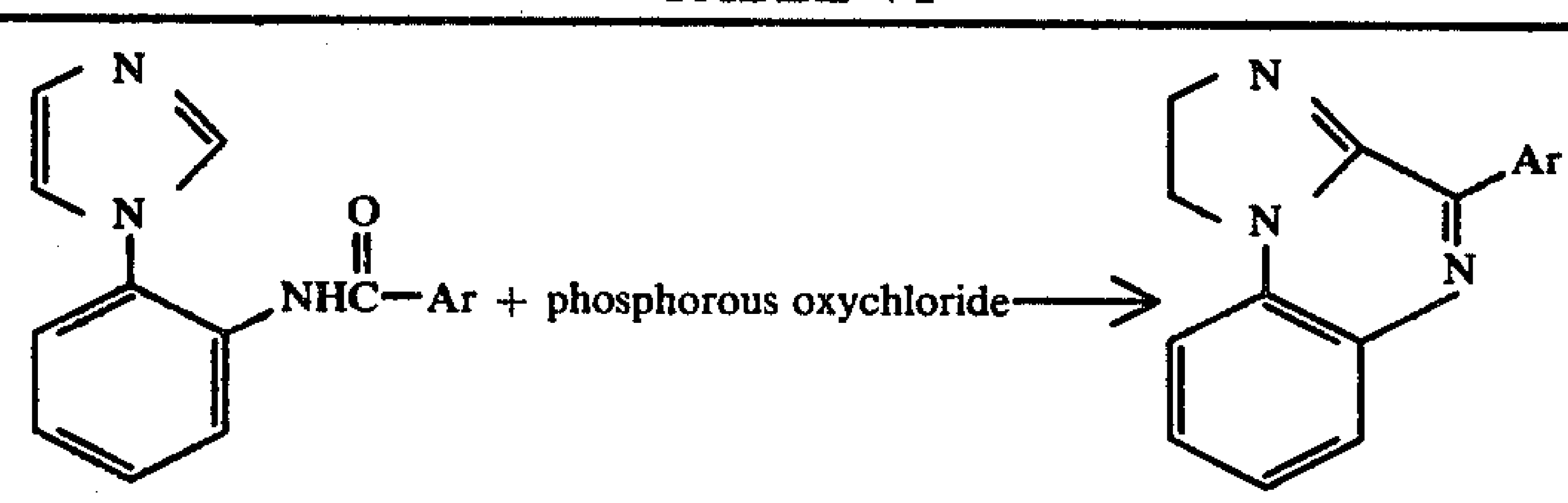
4-alkylimidazo[1,2-a] quinoxalines

No.	R	% Yield	Recrystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
129		2.0	hexane	119–120.5	311(11,400)	C,76.46 H, 6.82 N,16.72	76.65 6.76 16.58
130		0.8	isopropyl ether	133–135	312(11,700)	C,77.39 H, 5.68 N,16.92	77.20 6.13 16.76

Notes:
a. A.M. Siminov and I.G. Urykina, Khim. Geterot Soedin., 7,570(1971) report this compound has an mp of 124° with $\lambda_{max.}^{MeOH}$ (Am) = 315 (10,700).
b. Purified by sublimation at 90°/0.15 mm Pressure.
c. Purified by distillation at 174°–184°/0.40 mm P.

4-Arylimidazo[1,2-a]quinoxalines (Table VI) were prepared and isolated according to the general method described for the 4-alkylimidazo[1,2-a]quinoxalines, except as noted in Table VI.

TABLE VI



4-Arylimidazo[1,2-9]quinoxalines

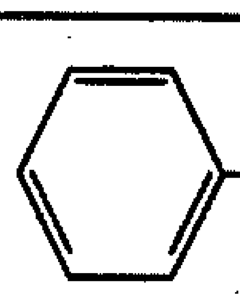
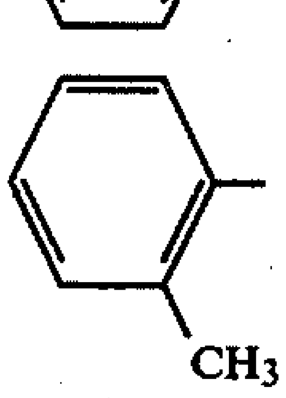
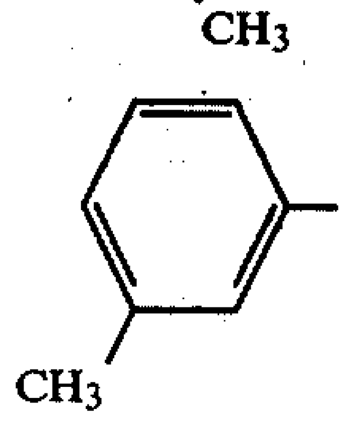
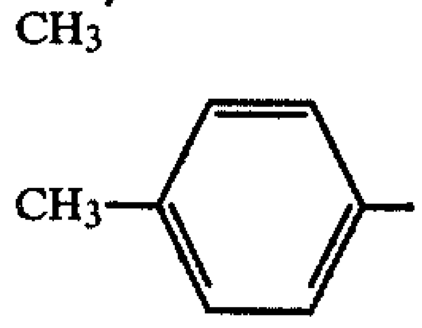
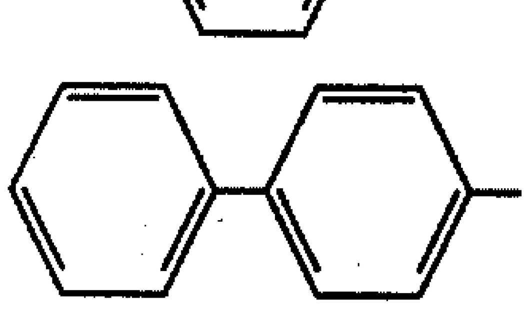
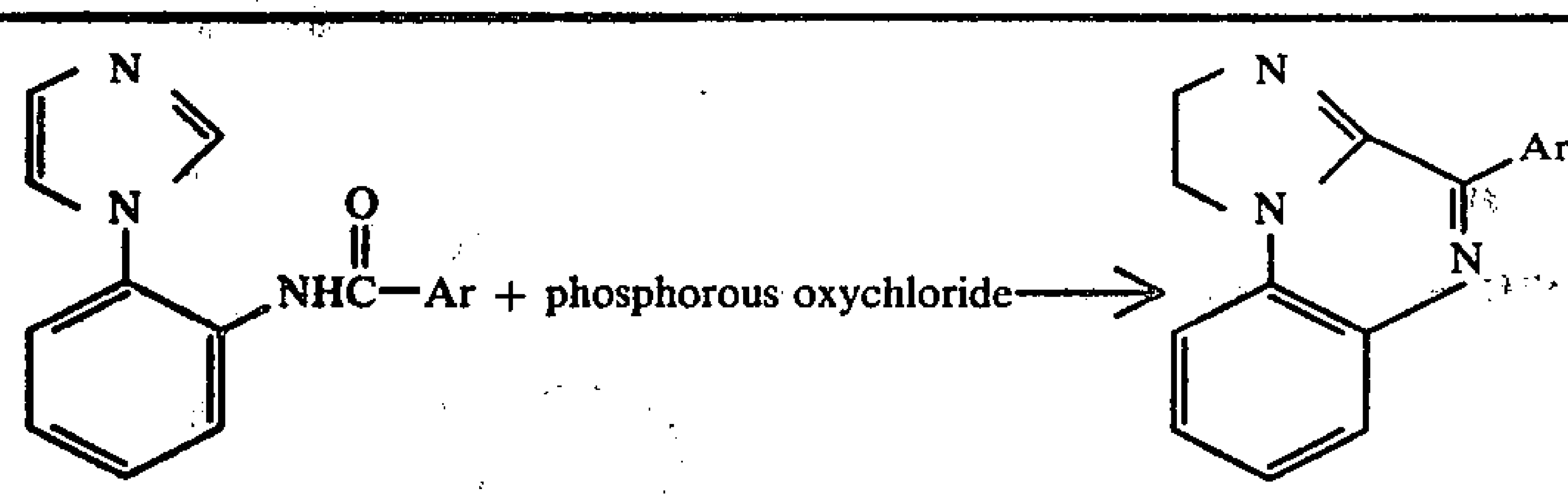
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
131	 a.	34.8	benzene	145–147	328(14,100)	C,78.35 H, 4.52 N,17.13	78.70 4.38 16.90
132		37.2	toluene-isopropanol	149–150.5	334(22,650)	C,78.74 H, 5.05 N,16.20	78.80 5.08 16.27
133		35.9	isopropanol-isopropyl ether	112–114	329(14,400)	C,78.74 H, 5.05 N,16.20	78.53 5.19 16.20
134		47.1	isopropanol	119–120	329(18,100)	C,78.74 H, 5.05 N,16.20	78.32 4.73 15.93
135		37.8	isopropanol	136–137	331(27,780)	C,82.22 H, 4.70 N,13.07	82.06 4.38 12.89

TABLE VI-continued



4-Arylimidazo[1,2-9]quinoxalines

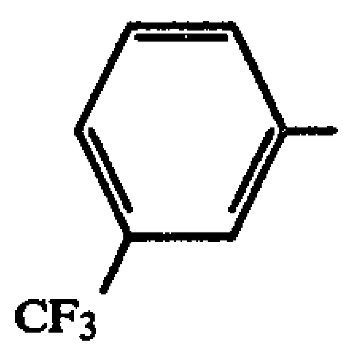
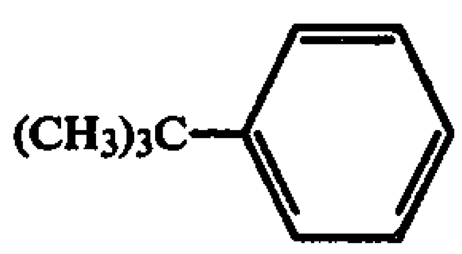
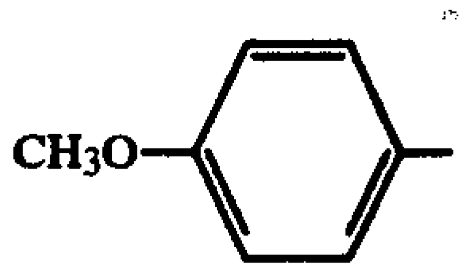
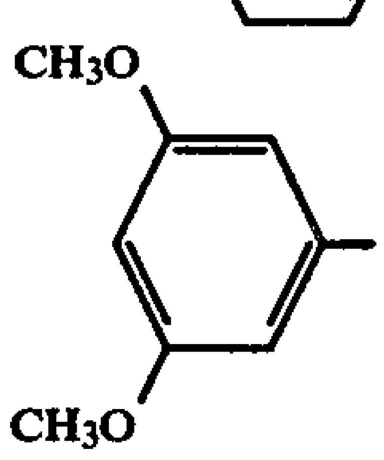
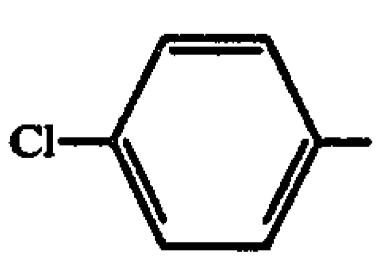
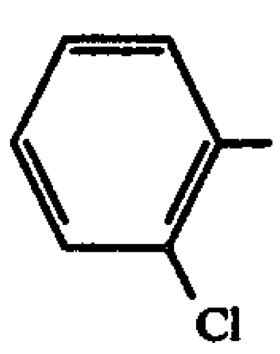
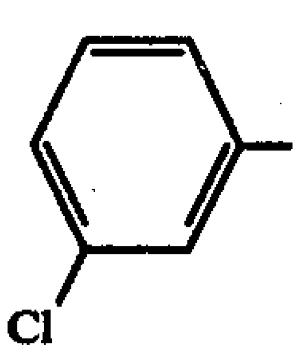
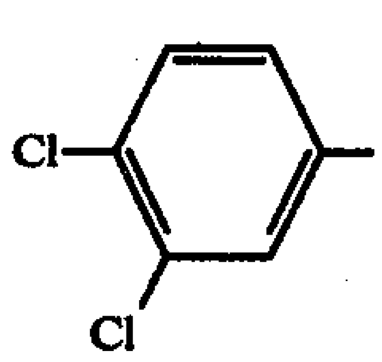
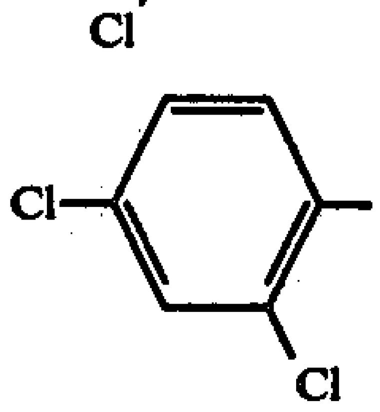
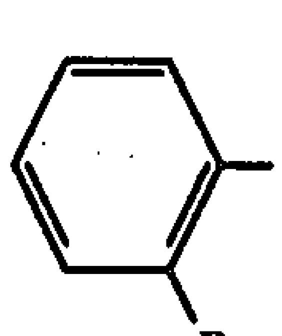
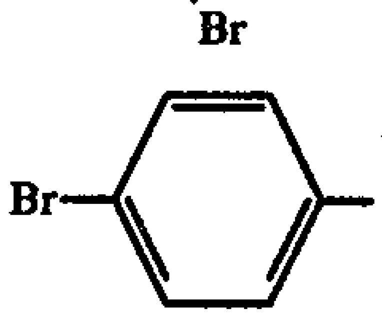
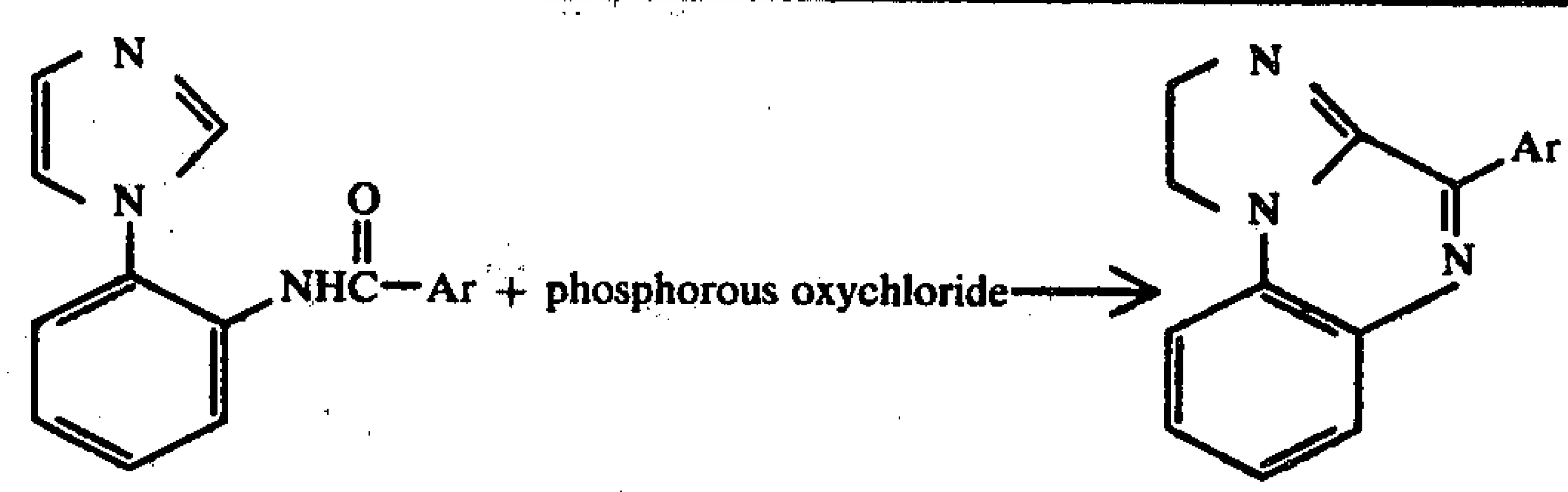
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
136		47.0	isooctane	112–113	332(10,411)	C,65.18 H, 3.22 N,13.41	65.03 3.10 13.62
137		56.7	hexanes	105–107	329(20,354)	C,79.70 H, 6.35 N,13.94	79.50 6.58 13.84
138		37.2	isopropanol-toluene	149–150.5	334(22,650)	C,74.17 H, 4.76 N,15.26	74.18 4.79 15.33
139		51.5	isopropanol	136–138	329(16,600)	C,70.81 H, 4.95 N,13.76	70.61 5.06 13.56
140		31.5	ethanol	173–175	328(16,280)	C,68.70 H, 3.60 N,15.02	69.06 3.28 15.08
141		6.8	benzene-hexanes	166–168	331(10,300)	C,68.70 H, 3.60 N,15.02	68.77 3.48 14.87
142		35.2	isopropanol	133–134	330(14,000)	C,68.70 H, 3.60 N,15.02	68.43 3.45 14.89
143		61.9	toluene	215–217.5	333(16,530)	C,61.16 H, 2.89 N,13.37	60.94 2.82 13.50
144		3.4	carbon tetra-chloride	168–170	321(13,030)	C,61.17 H, 2.89 N,13.37	60.61 2.85 13.57
145		24.1	dimethyl-formamide-water	161.5–164.5	319(10,200)	C,59.28 H, 3.11 N,12.96	58.75 3.03 12.90
146		13.4	dimethyl-formamide-water	172	329(12,900)	C,59.28 H, 3.11 N,12.96	59.34 3.13 13.23

TABLE VI-continued



4-Arylimidazo[1,2-9]quinoxalines

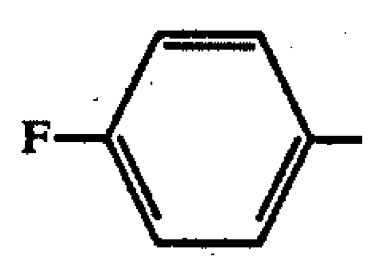
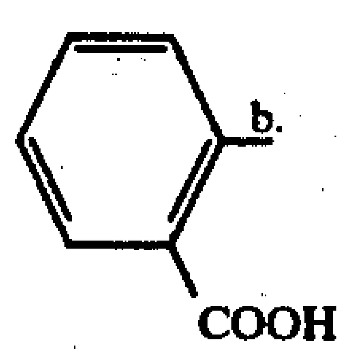
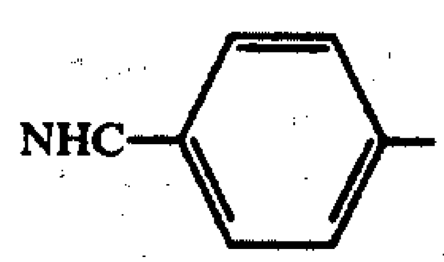
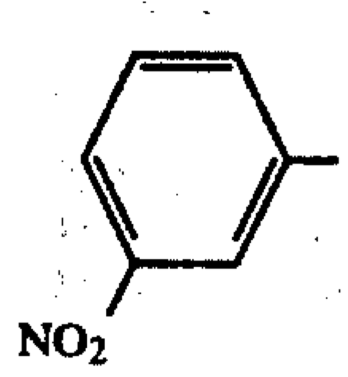
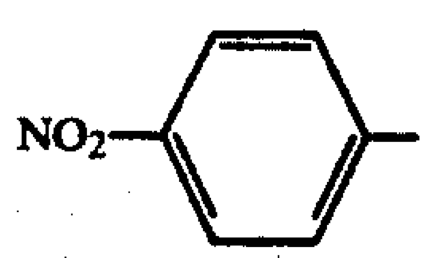
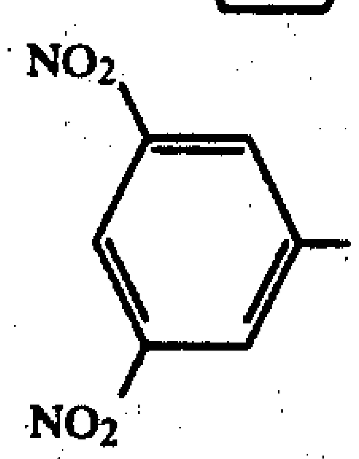
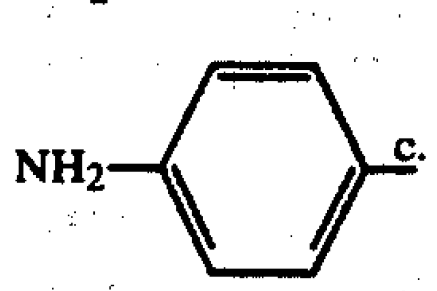
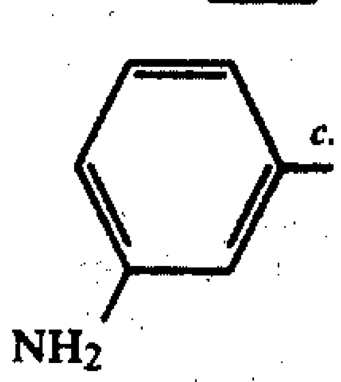
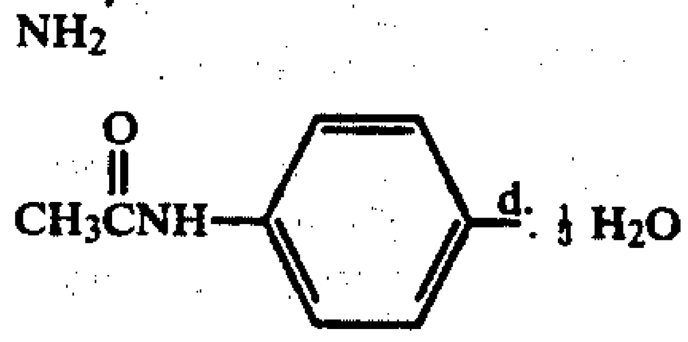
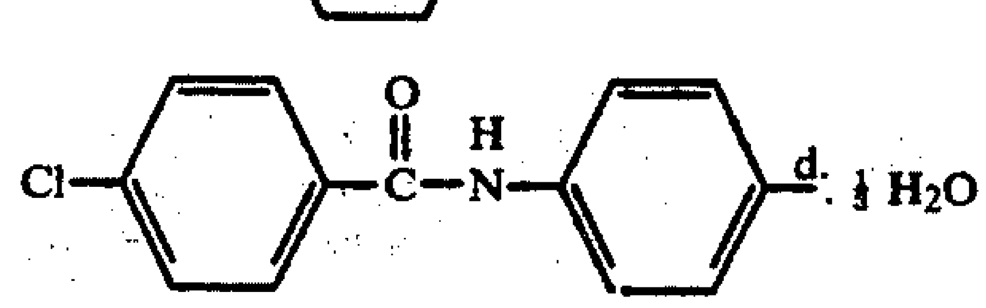
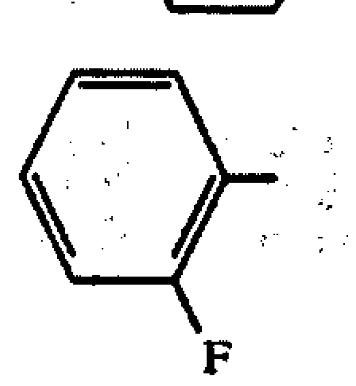
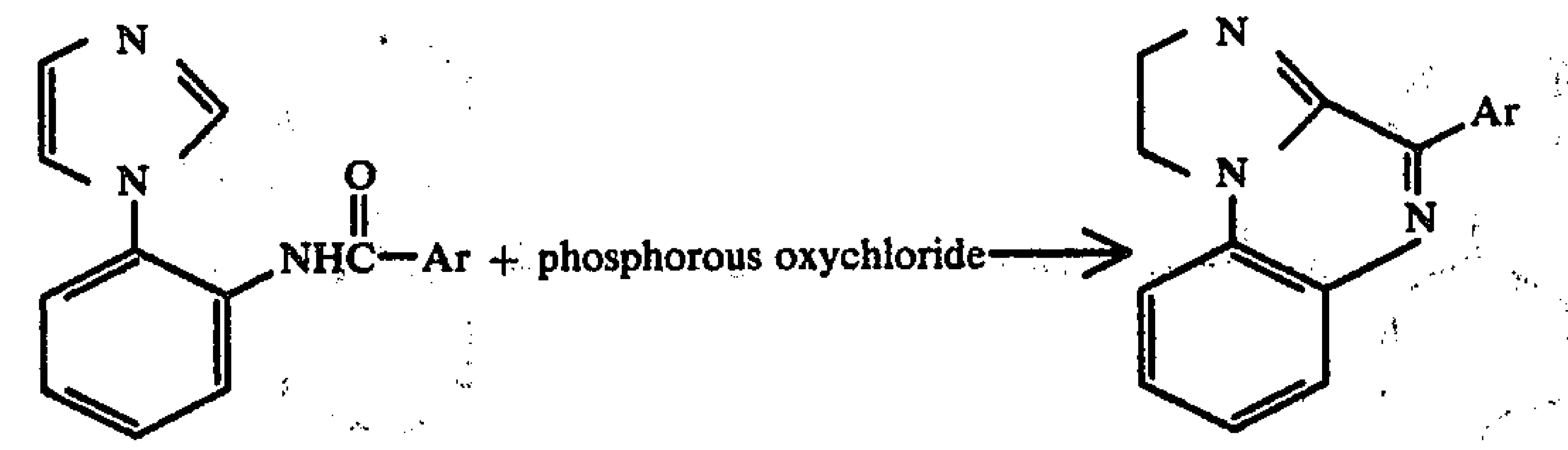
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
147		39.1	isopropanol	183-185	328(14,500)	C,72.99 H, 3.83 N,15.96	73.00 4.06 15.77
148		15.0	ethanol	190-192	222(48,000)	C,70.58 H, 3.83 N,14.52	70.54 3.71 14.67
149		53.3	dimethyl-formamide-water	257.5-259.5	335(14,900)	C,75.54 H, 3.73 N,20.73	75.15 3.85 20.66
150		59.8	2-ethoxyethanol	220.5-222.5	333(13,850)	C,66.20 H, 3.47 N,19.30	66.10 3.48 19.53
151		40.3	toluene	249-252	346(15,269)	C,66.20 H, 3.47 N,19.30	66.10 3.44 19.28
152		52.5	dimethyl-formamide	283-285	340(10,880)	C,57.30 H, 2.71 N,20.89	57.08 2.74 21.11
153		75.7	dimethyl-formamide-water	198-199.5	369(23,470)	C,73.83 H, 4.65 N,21.53	73.48 4.69 21.54
154		61.9	dimethyl-formamide-water	130-133	326(14,830)	C,73.83 H, 4.65 N,21.53	73.56 4.78 21.69
155		58.0	ethylacetate-hexane	214-217	342(27,700)	C,68.88 H, 4.66 N,17.85	68.46 4.99 17.76
156		13.9	dimethyl-formamide-water	237.5-240	345(32,350)	C,68.24 H, 3.90 N,13.84	68.54 3.90 14.00
173		32.3	ethanol	155-157	321(13,090)	C,72.99 H, 3.83 N,15.96	72.44 3.83 16.14

TABLE VI-continued



4-Arylimidazo[1,2-9]quinoxalines

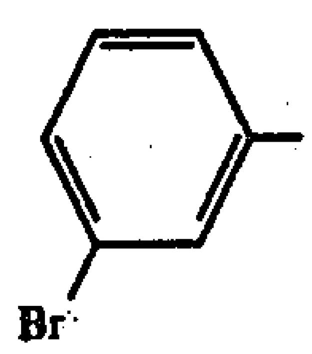
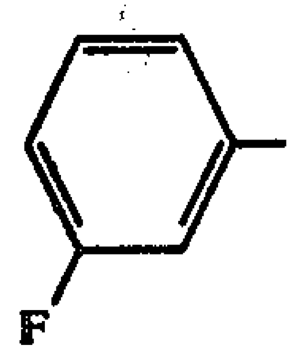
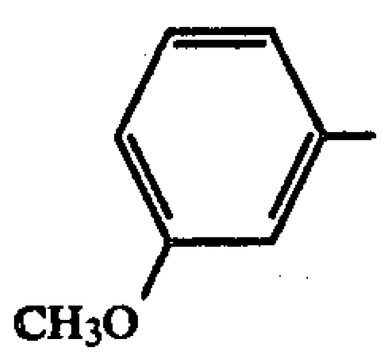
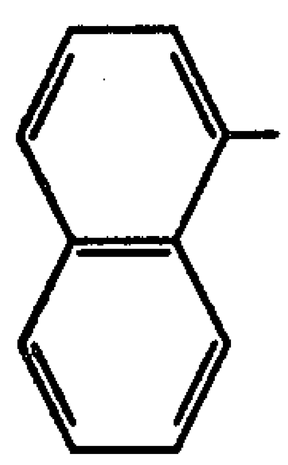
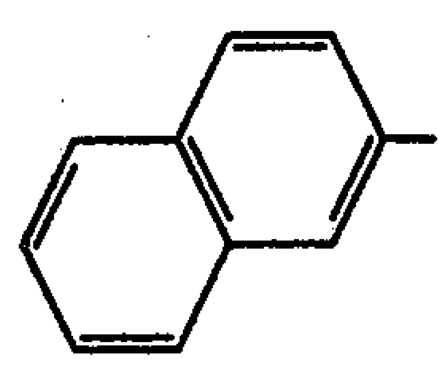
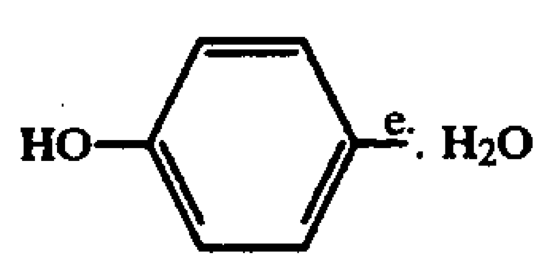
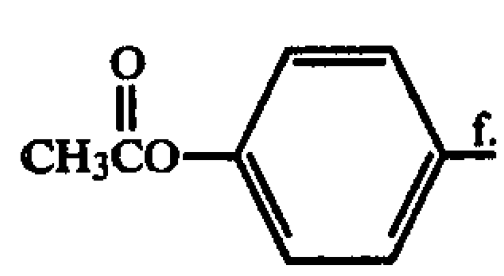
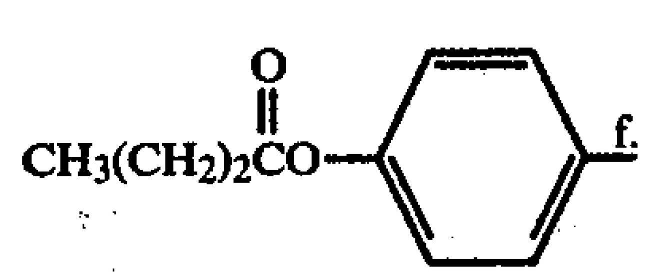
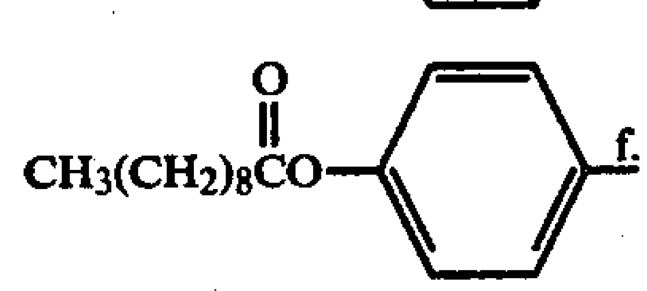
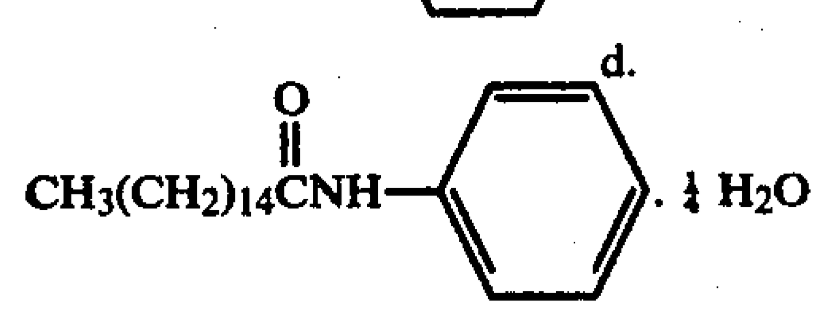
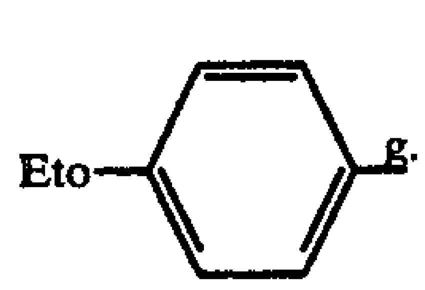
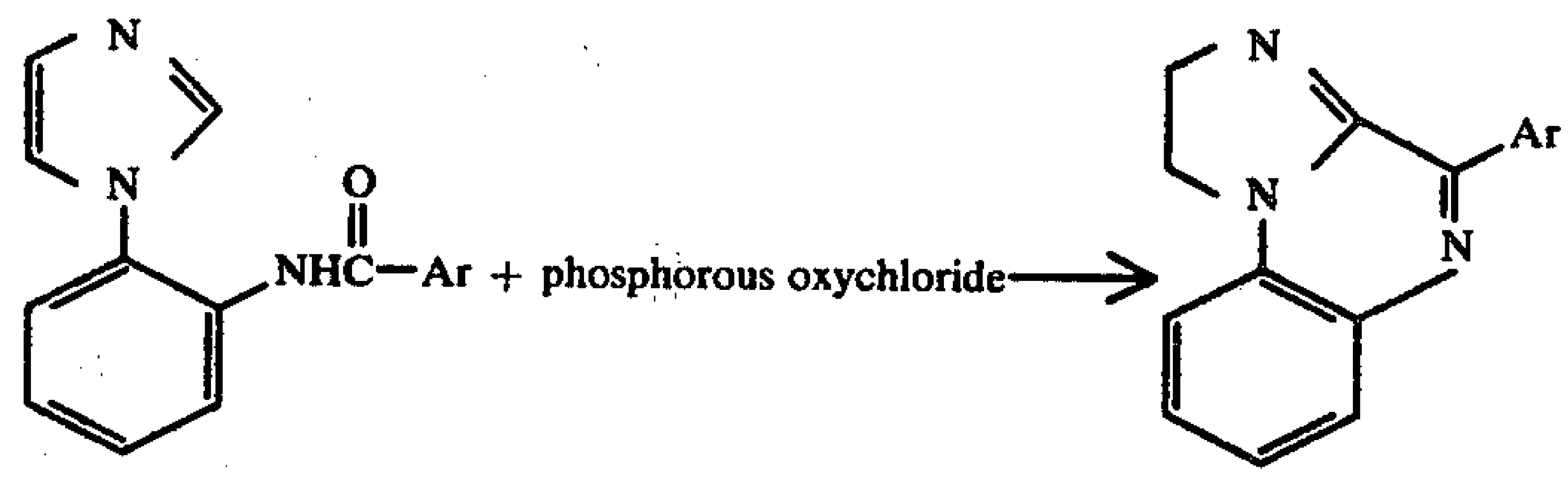
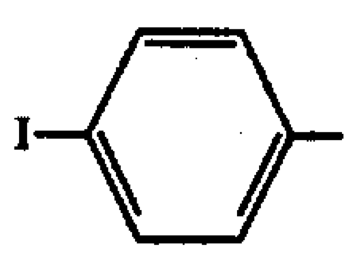
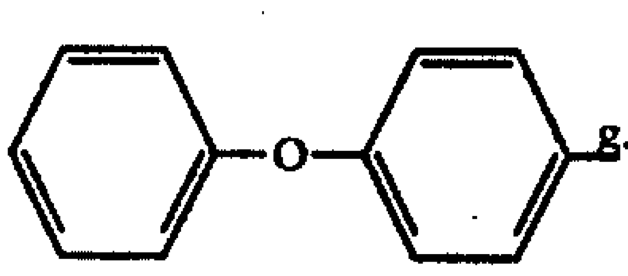
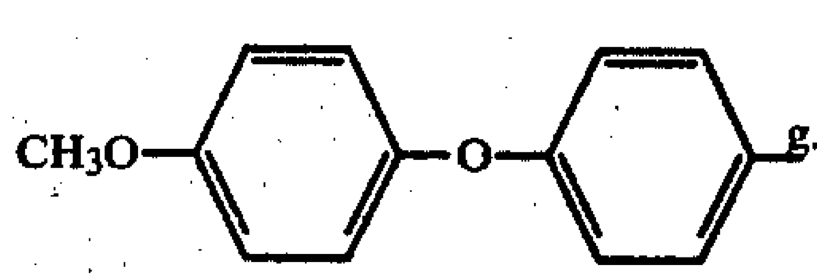
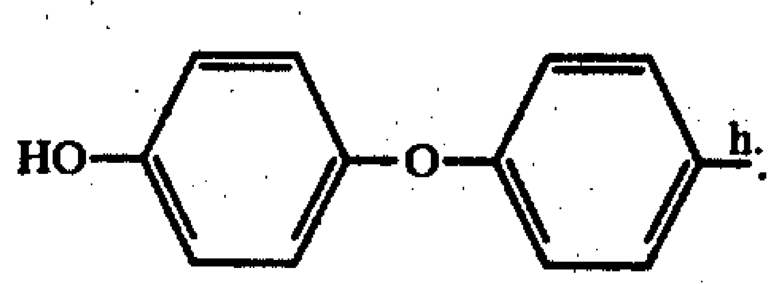
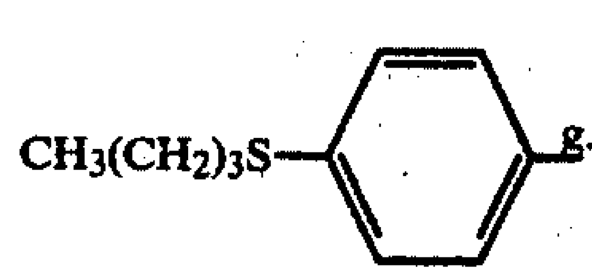
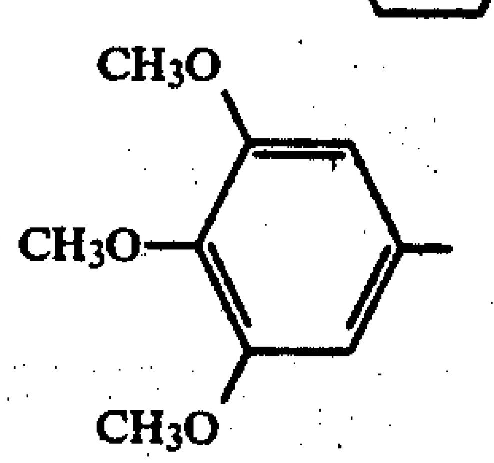
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
157		56.6	dimethyl-formamide-water	134.5–136	332(14,260)	C,59.28 H, 3.11 N,12.96	59.25 3.04 13.11
158		47.5	dimethyl-formamide-water	132.5–134	330(13,970)	C,72.99 H, 3.83 N,15.96	73.00 3.79 15.84
159		52.7	ethanol	113–114.5	329(16,500)	C,74.17 H, 4.76 N,15.26	74.09 4.71 15.05
160		10.62	chloroform	159–161.5	323(15,290)	C,81.34 H, 4.43 N,14.23	81.29 4.41 14.22
161		43.2	benzene	154.5–156.5	340(21,800)	C,81.34 H, 4.44 N,14.23	81.19 4.57 13.92
162		25.4	isopropanol	210–215	343(23,800)	C,68.81 H, 4.69 N,15.04	68.99 4.63 14.92
163		84.2	ethanol	158–160	333(14,950)	C,71.28 H, 4.32 N,13.85	71.31 4.44 13.85
164		80.3	ethanol	116–118	335(15,100)	C,72.49 H, 5.17 N,12.68	72.38 5.42 12.36
165		62.6	ethanol	90.5–93.5	335(15,100)	c,75.15 H, 7.03 N,10.11	74.87 7.16 9.94
166		45.85	chloroform	154–155.5	344(27,240)	C,76.38 H, 8.51 N,11.14	76.58 8.35 10.81
193		29.80	ethanol	150–152	342(22,900)	C,74.72 H, 5.23 N,14.52	74.37 5.17 14.33

TABLE VI-continued



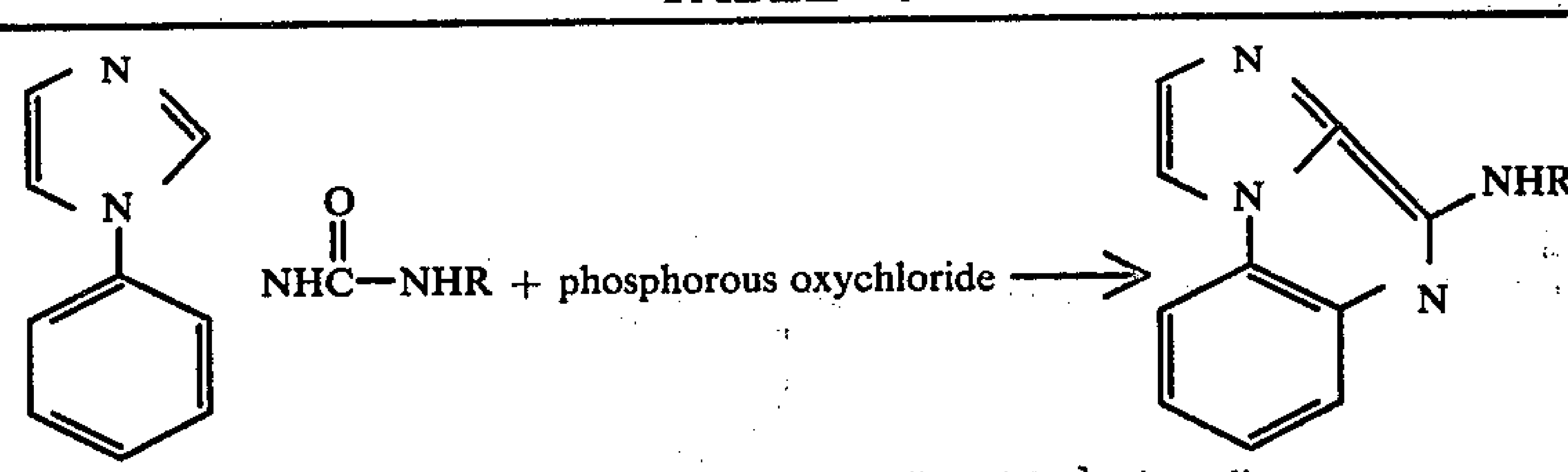
4-Arylimidazo[1,2-9]quinoxalines

No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
196		8.2	dimethyl-formamide-water	178–181	330(27,300)	C,51.77 H, 2.72 N,11.32	51.89 2.68 11.46
219	 g.	37.1	toluene	151.5–153.5	333(21,000)	C,78.32 H, 4.48 N,12.45	78.32 4.63 12.22
220	 g.	35.1	benzene	151.5–153.5	337(22,200)	C,75.19 H, 4.66 N,11.44	75.42 4.58 11.46
221	 h. ½ H_2O	33.3	ethanol-water	>330°	343(22,700)	C,72.92 H, 4.45 N,11.60	73.21 4.31 11.74
222	 g.	28.2	ethanol	83–85	348(24,600)	C,72.04 H, 5.74 N,12.60	71.64 5.68 12.62
194		22.6	toluene	164–165.5	339(19,400)	C,68.05 H, 5.11 N,12.53	67.70 5.03 12.32

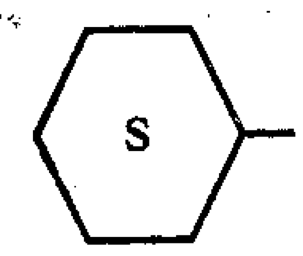
a. U.S. Pat. No. 3,887,566 describes this compound as having a m.p. of 154–157° C.
b. Prepared by refluxing aquimolar amounts of the 2-aminophinyl-imidazole and phthalic anlydride in toluene for one and one-half hours. Upon cooling, the product separated out of solution.
c. Prepared by catalytic hydrogenation with 10% palladium on carbon of a dimethylformamide solution of the nitro analog; crude product precipitated with water.
d. Prepared by treating compound 153 in pyridine with the appropriate acid chloride followed by precipitation with water.
e. Prepared by HI cleavage of compound No. 138.
f. Prepared by treating the lithium salt of compound No. 162 with the appropriate acid chloride in DMF followed by precipitation with water.
g. Prepared by treating compound No. 151 with the appropriate nucleo-phile according to the method of Kornblum et al, J. Org. Chem., 41, 1560(1976).
h. Prepared by HI cleavage of compound 220.

The 4-Alkylaminoimidazo[1,2-a]quinoxalines (Table VII) were prepared by treating the corresponding alkylureylenes (Table III) with phosphorous oxychloride and pyridine during one-half hour at reflux temperatures. The reaction mixture was poured into cold water and the excess pyridine was removed by azeotropic distillation. The crude product was dissolved in chloroform and pass through an alumina columa. After evaporation of the chloroform, the solid was crystallized from the indicated solvent and obtained in the indicated yield.

TABLE VII

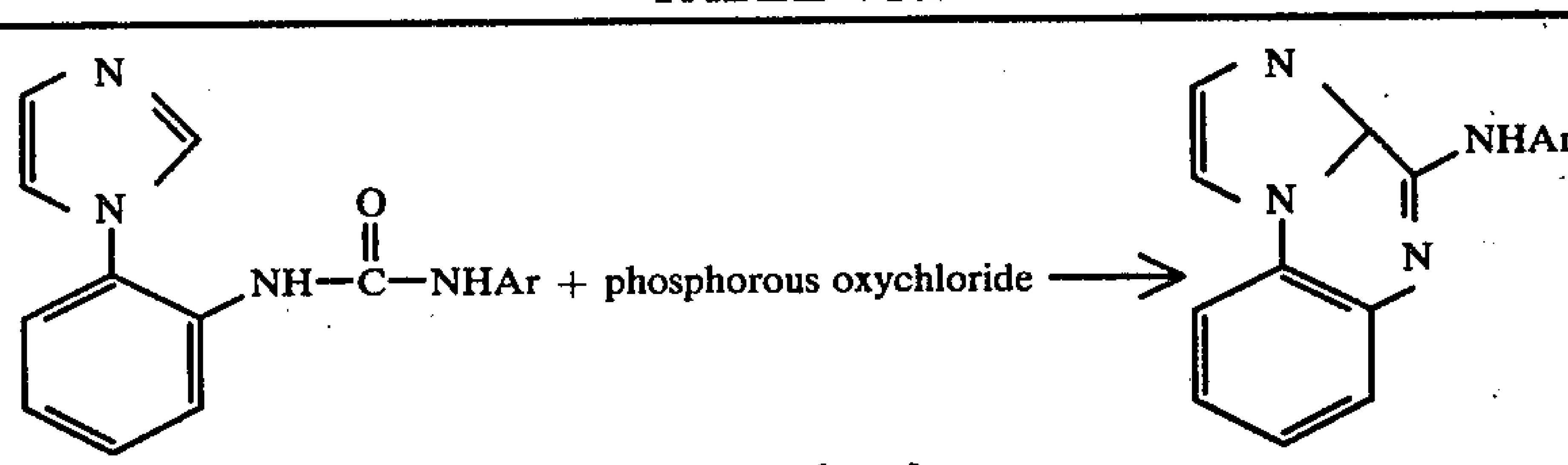


4-Alkylaminoimidazo[1,2-a]quinoxalines 1,2-a}quinoxalines

No.	R	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
167		4.89	hexane	98.5–101.5	335(11,700)	C,72.15 H, 6.81 N,21.04	72.02 6.75 20.81
168	$CH_3(CH_2)_2CH_2$—	28.33	isopropyl ether	102–104	332(11,480)	C,69.97 H, 6.71 N,23.31	70.12 6.71 23.21
169	$CH_3(CH_2)_2$—	7.5	isopropyl ether	72–74	317(15,800)	C,69.00 H, 6.24 N,24.76	69.14 6.35 24.60

4-Arylaminoimidazo[1,2-a]quinoxalines (Table VIII) were prepared by treating the corresponding arylaureylenes (Table IV) with an equimolar amount of phosphorous oxychloride in refluxing pyridine during one hour. The cooled reaction mixture was stirred into cold water, and the crude solid which separated was dissolved in chloroform, dried and passed through an alumina column. The chloroform was evaporated and the crude solid was crystallized as indicated in Table VIII.

TABLE VIII



4-Arylaminoimidazo{1,2-a}quinoxalines

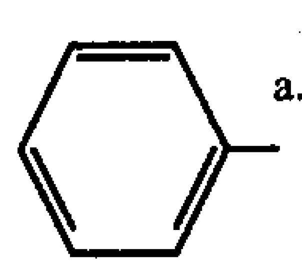
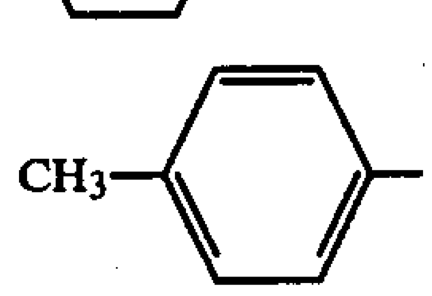
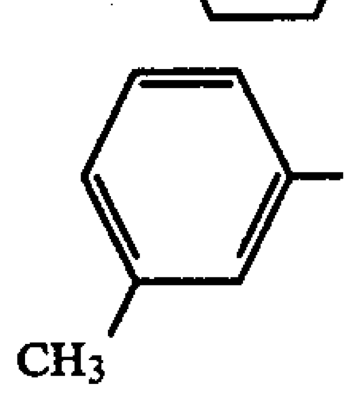
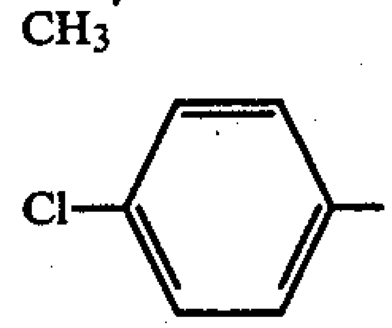
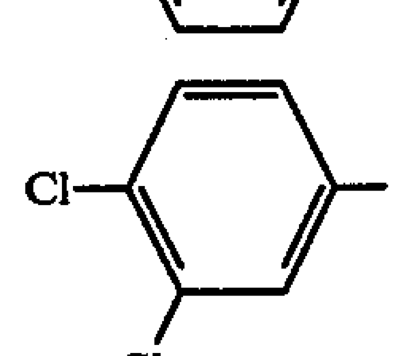
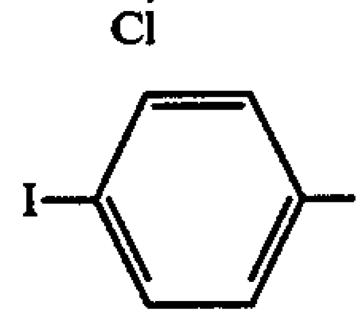
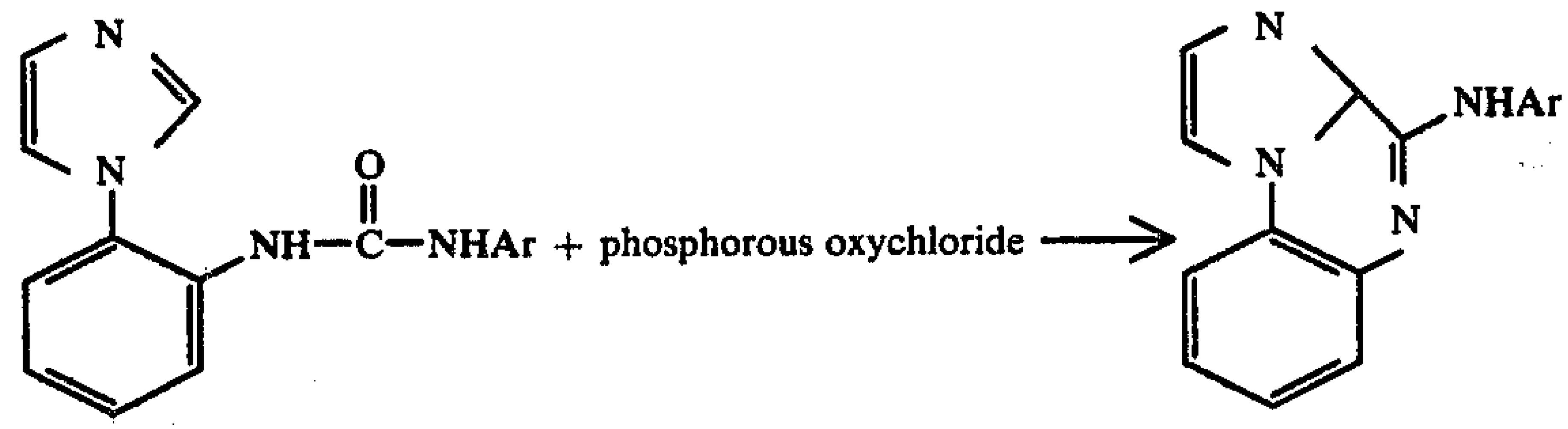
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
170	 a.	7.2	ethanol-water	120–123	304(13,800)	C,72.57 H, 4.76 N,21.16	72.67 4.71 20.88
171		13.1	methanol-chloroform	151	334(20,700)	C,74.43 H, 5.14 N,20.42	74.16 5.06 20.09
172		11.7	methanol-chloroform	153–155	330(20,200)	C,74.43 H, 5.14 N,20.42	73.23 5.26 20.02
174		13.6	methanol-chloroform	176.5–178	330(22,200)	C,65.26 H, 3.75 N,19.02	65.04 3.77 18.91
175		10.9	methanol-chloroform	178.5–180.5	334(33,600)	C,58.38 H, 3.06 N,17.02	58.15 3.06 17.09
176		18.2	toluene-chloroform	193.5–195	332(4,500)	C,49.76 H, 2.87 N,14.51	49.72 3.10 14.39

TABLE VIII-continued



4-Arylaminoimidazo{1,2-a}quinoxalines

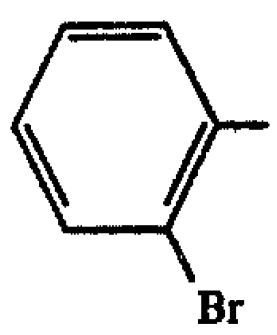
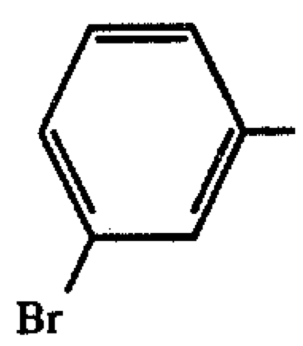
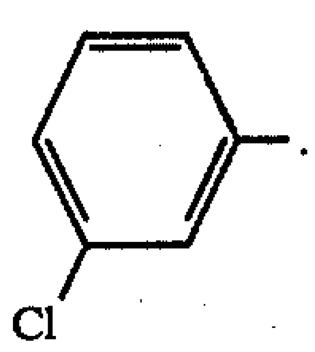
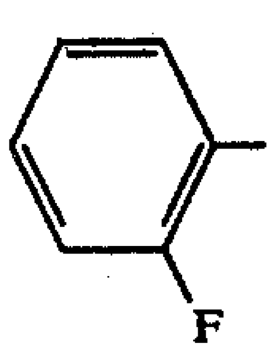
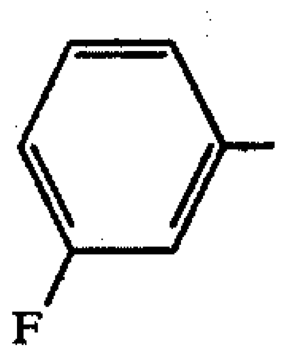
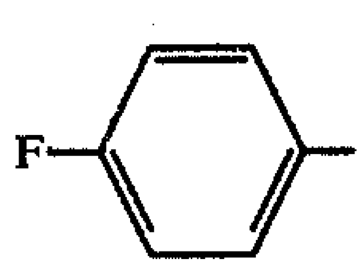
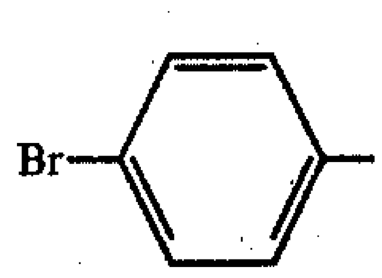
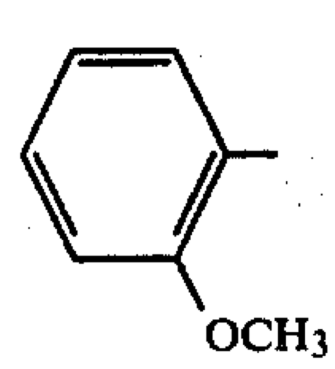
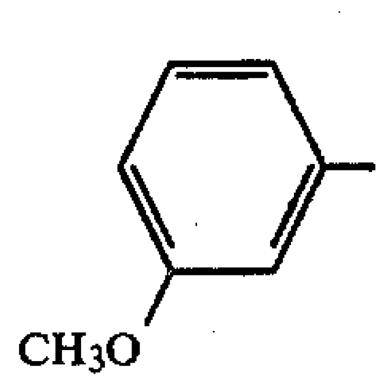
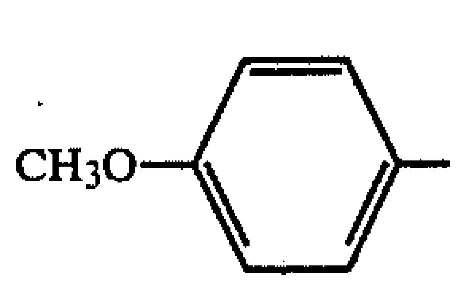
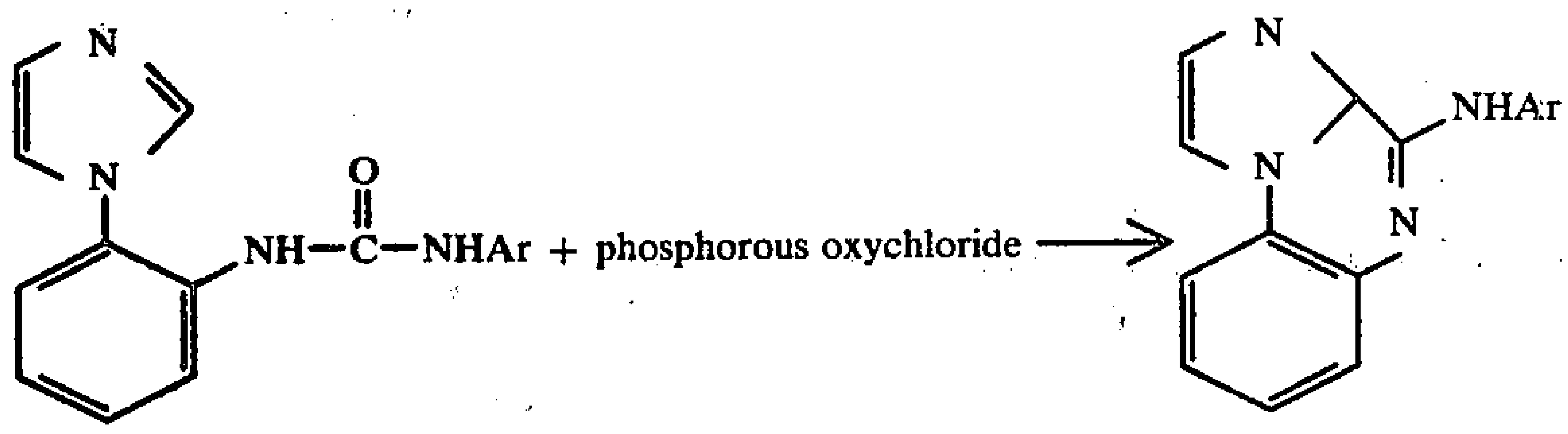
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
177		11.5	ethanol	196.5–198.5	324(16,600)	C,56.66 H, 3.27 N,16.52	56.69 3.24 16.43
178		15.0	methanol-chloroform	184–185.5	329(24,100)	C,56.66 H, 3.27 N,16.52	56.26 3.20 16.54
179	 . ½ H_2O	10.52	dimethylformamide water	122–124	343(19,600)	C,63.27 H, 3.98 N,18.45	62.94 4.19 18.58
180		13.0	ethanol-dimethylformamide	139	339(19,810)	C,69.05 H, 3.98 N,20.13	68.88 4.02 20.13
181		9.4	isopropanol	148.5–149.5	343(20,230)	C,69.05 H, 3.98 N,20.13	68.92 4.00 20.14
182		3.1	isopropanol	139.5–141	331(18,030)	C,69.05 H, 3.98 N,20.13	68.50 3.92 19.86
183		16.58	dimethylformamide-water	166–168.5	347(21,730)	C,56.66 H, 3.27 N,16.52	56.31 3.25 16.56
184		11.4	dimethylformamide-water	207–209	366(22,410)	C,70.33 H, 4.86 N,19.30	70.61 5.11 19.11
185		8.3	dimethylformamide-water	116.5–117.5	335(21,820)	C,70.33 H, 4.86 N,19.30	70.16 5.28 19.31
186		14.12	dimethylformamide-water	147–149	339(18,540)	C,70.33 H, 4.86 N,19.30	70.14 4.98 19.09

TABLE VIII-continued



4-Arylaminoimidazo{1,2-a}quinoxalines

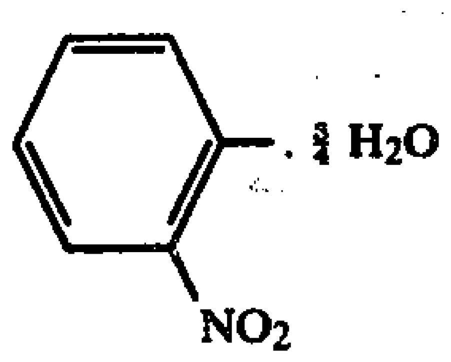
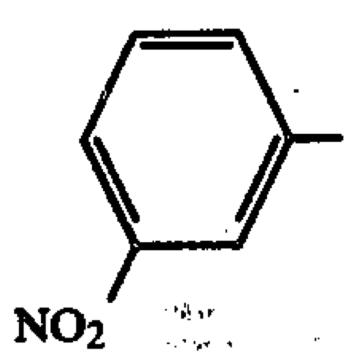
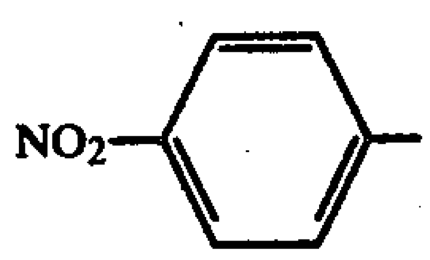
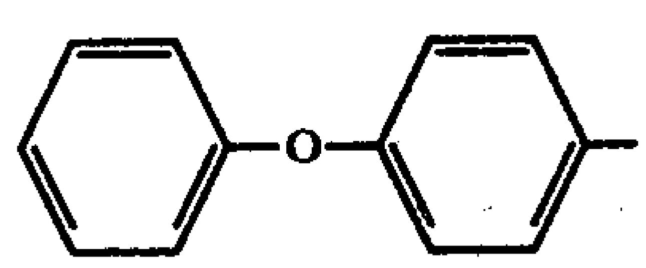
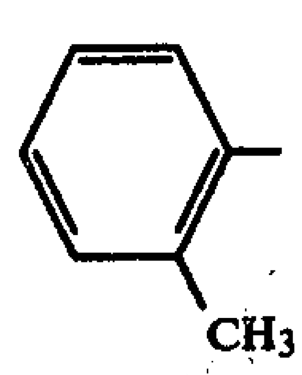
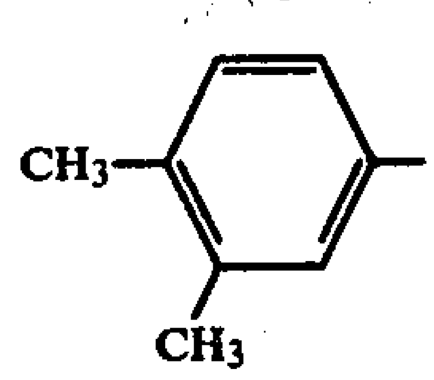
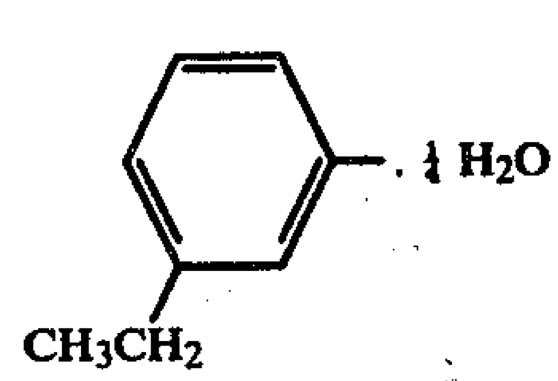
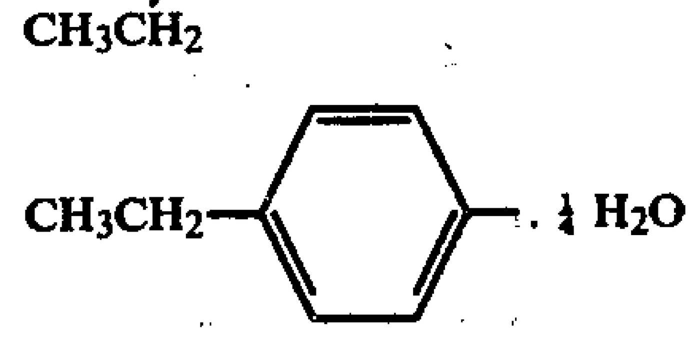
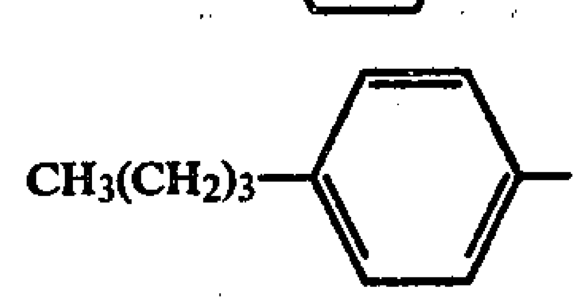
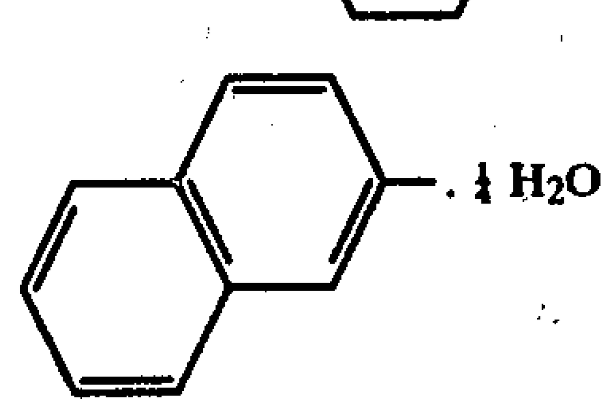
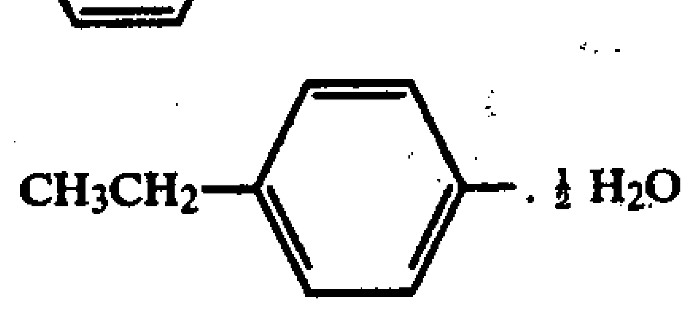
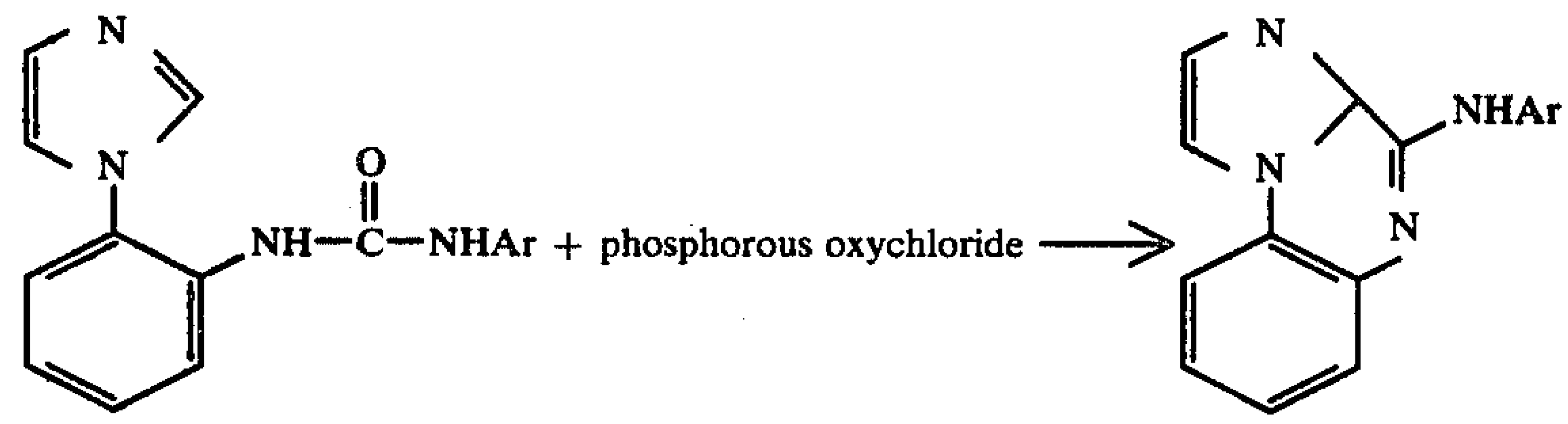
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
187		2.0	isopropanol-dimethylformamide	195–197	341(20,370)	C,60.28 H, 3.95 N,21.97	60.21 3.88 21.63
188		36.4	dimethylformamide-water	241–243.5	400(8,960)	C,62.95 H, 3.63 N,22.94	62.62 3.63 22.68
189		33.1	dimethylformamide-water	323–324.5	368(23,670)	C,62.95 H, 3.63 N,22.94	62.73 3.73 22.81
195		11.61	dimethylformamide-water	138.5–141	335(22,900)	C,74.99 H, 4.58 N,15.90	75.02 4.66 75.02
197		5.52	dimethylformamide-water	143–145	330(18,000)	C,74.43 H, 5.15 N,20.42	74.63 5.16 20.09
198		10.91	dimethylformamide	163.5–165.5	337(18,800)	C,74.98 H, 5.59 N,19.43	74.69 5.56 19.43
199		15.29	dimethylformamide-water	81–83	333(20,800)	C,73.83 H, 5.51 N,19.13	73.87 5.49 18.88
200		13.81	dimethylformamide-water	124.5–127	335(23,200)	C,73.83 H, 5.51 N,19.13	74.14 5.47 19.02
201		16.96	isopropanol-water	89.5–91.5	335(21,000)	C,73.83 H, 5.51 N,19.13	74.14 5.47 19.02
202		11.50	methanol-chloroform	187–190	342(24,200)	C,76.29 H, 4.56 N,17.80	76.58 4.52 17.58
203		12.50	dimethylformamide-water	120.5–123	340(20,300)	C,68.99 H, 5.15 N,17.88	68.32 5.32 17.61

TABLE VIII-continued



4-Arylaminoimidazo{1,2-a}quinoxalines

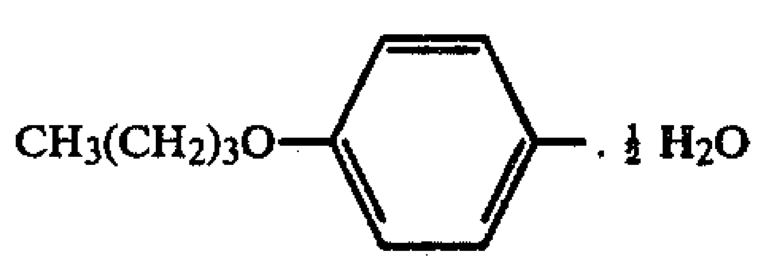
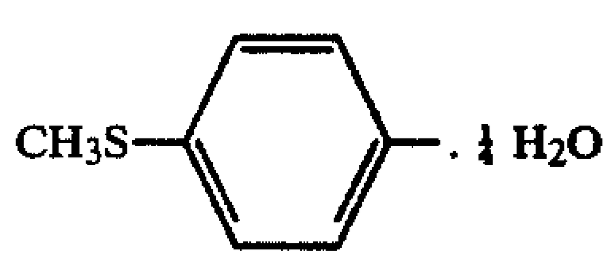
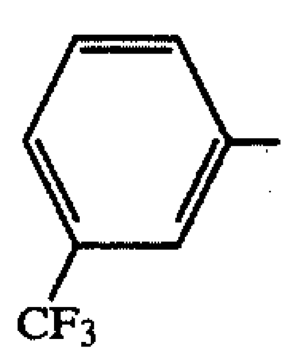
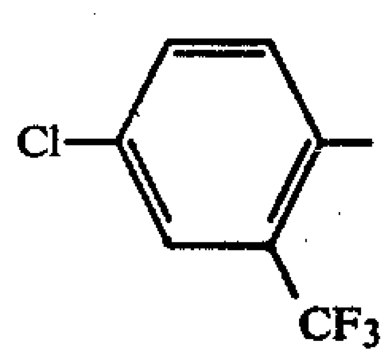
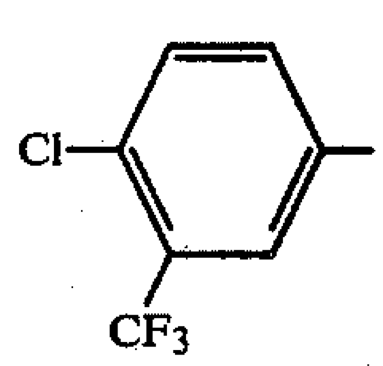
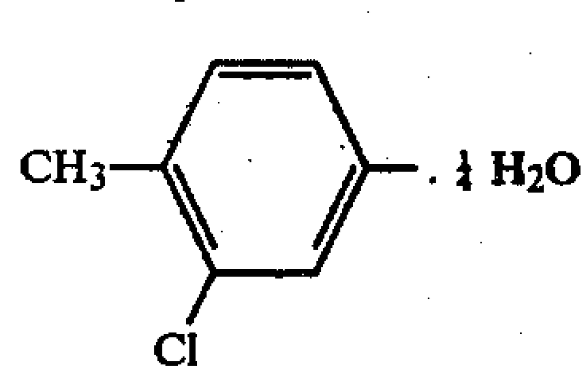
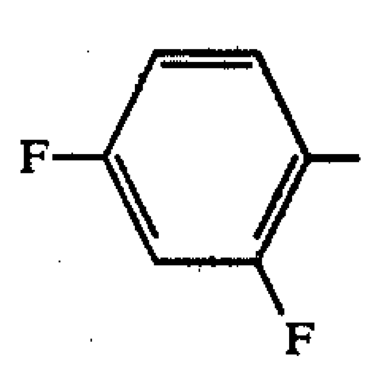
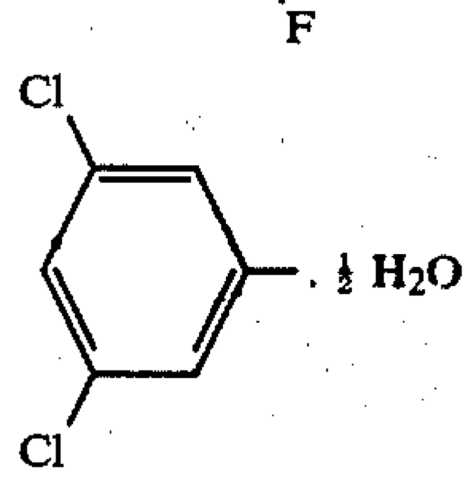
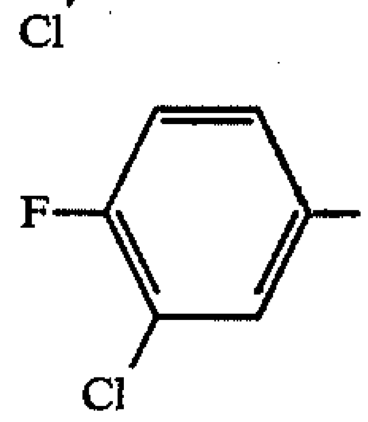
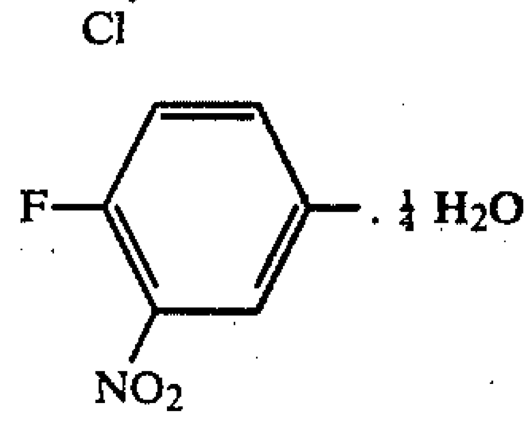
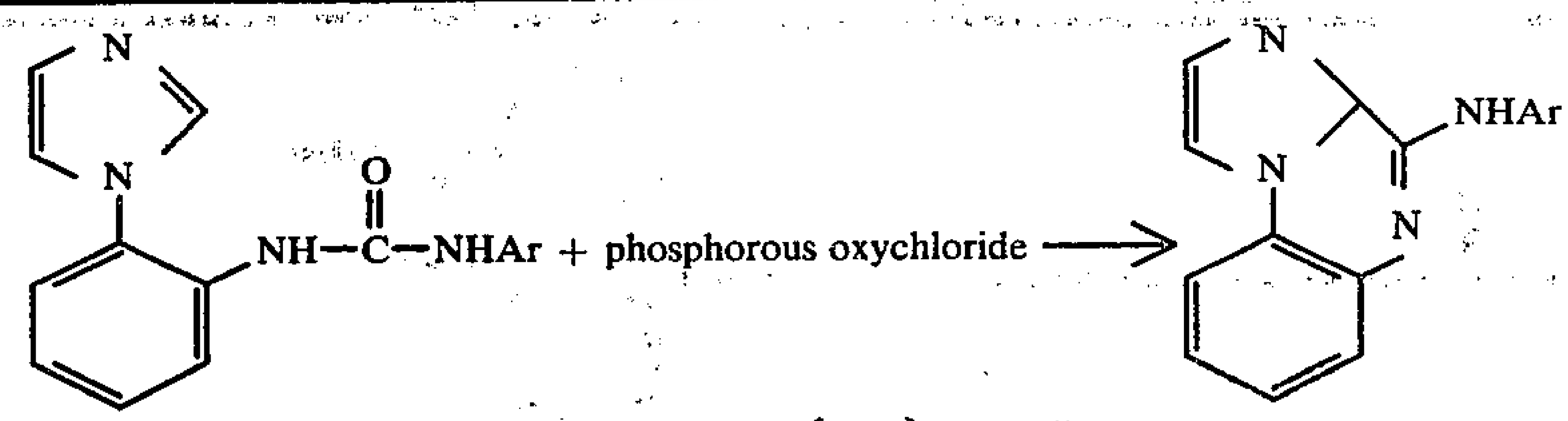
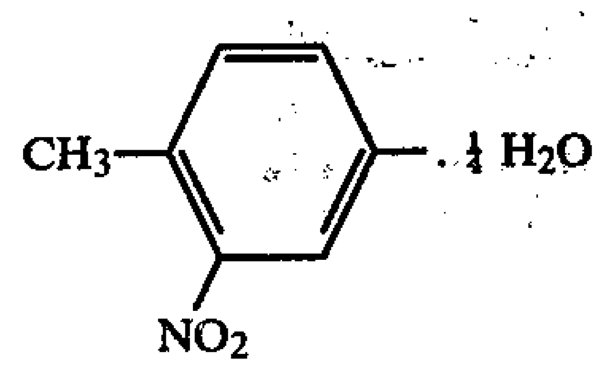
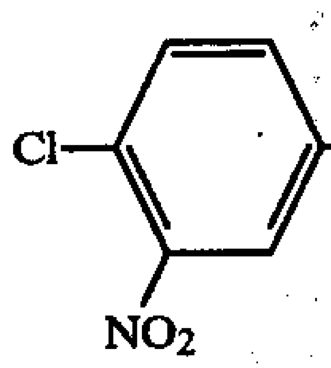
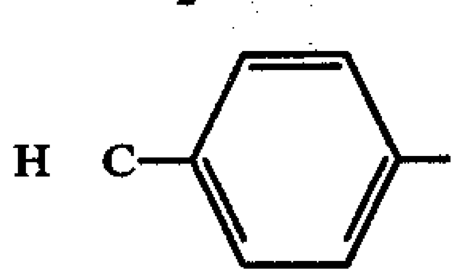
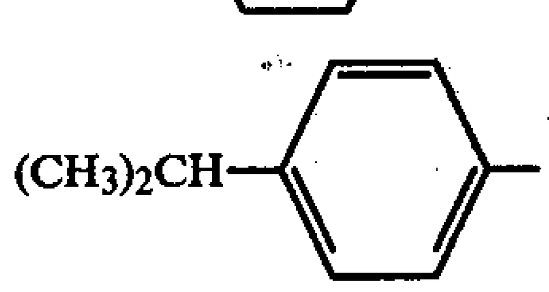
No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
204		21.39	dimethylformamide-water	102.5–107	340(19,600)	C,62.20 H, 3.38 N,17.07	61.56 3.34 17.46
205		8.5	dimethylformamide-water	90–97	341(26,400)	C,65.68 H, 4.62 N,18.02	65.56 4.57 17.88
206		21.39	dimethylformamide-water	129–130	347(20,300)	C,62.20 H, 3.38 N,17.07	61.56 3.34 17.46
207		11.49	dimethylformamide-water	178.5–179.5	324(25,500)	C,56.29 H, 2.78 N,15.45	55.86 2.72 15.37
208		7.52	dimethylformamide-water	172.5–173.5	345(24,900)	C,56.29 H, 2.78 N,15.45	56.13 2.72 15.35
209		15.18	dimethylformamide-water	170–172	332(23,800)	C,65.18 H, 4.18 N,17.89	65.35 4.15 17.91
210		13.56	dimethylformamide-water	171.5–173	337(17,300)	C,64.86 H, 3.40 N,18.91	64.92 3.51 19.09
211		10.78	dimethylformamide-water	259.5–261.5	342(23,200)	C,56.82 H, 3.28 N,16.57	56.76 3.07 16.57
212		7.22	dimethylformamide-water	198–200	343(18,400)	C,61.45 H, 3.22 N,17.92	61.35 3.27 17.81
213		3.04	methanol-chloroform	229–231	341(19,900)	C,58.63 H, 3.15 N,21.36	58.50 3.06 21.20

TABLE VIII-continued



4-Arylaminoimidazo{1,2-a}quinoxalines

No.	Ar	% Yield	Crystallization Solvent	m.p. °C.	λmax.(Am)	Analysis Calc'd	Analysis Found
214		4.18	methanol-chloroform	168–170	344(21,400)	C,63.06 H, 4.12 N,21.63	62.97 4.08 21.34
215		19.43	dimethylformamide-water	271–273	346(19,600)	C,56.57 H, 2.97 N,20.61	56.44 2.90 20.51
216		5.96	dimethylformamide-water	224–226.5	349(34,700)	C,70.48 H, 3.91 N,24.17	70.89 3.94 24.09
217		2.31	isopropanol	95–96.5	—	C,75.47 H, 6.00 N,18.53	75.08 6.34 18.53

Various compounds of this invention display anti-fungal and anti-yeast activity. Thus, for example, they have been found to be effective against such organisms as *Candida albicans* (ATCC No. 10231), *Candida tropicalis, Aspergillus niger* (ATCC No. 16404), *Trichophyton mentagrophytes* (ATCC No. 8757 and 9129), *Trichophyton rubrum* (ATCC No. 10218 and 14001) and *Trichophyton ajelloi.*

The antifungal activity of compounds of this invention indicate their usefulness against dermatomycosis such as tinea capitis, tinea favosa, tinea barbae, tinea corporis, tinea imbricata, tinea cruris, tinea pedis, tinea manus, tinea unquium and various types of candidiasis such as glossitis, stomatitis, chelitis, perleche, vaginitis and balanitis.

When the compounds of the present invention are used for antifungal medical purposes, they will usually be incorporated in a suitable pharmaceutical carrier. These antifungal preparations may take the form of solutions, lotions, creams, ointments, etc. The quantity of antifungal agent of this invention that will be contained in such preparations may vary somewhat. Ordinarily, however, it will constitute about 0.5% to 10.0% by weight based on the total weight of the preparation.

In Table IX below are listed the antifungal activity of a number of compounds encompassed in the present invention. These were determined by the agar dilution method as described in Chapters 2 and 3 of *Methods in Microbiology,* Vol. 7B, edited by J. R. Norris and D. W. Ribbons, Academic Press, New York, 1972.

TABLE IX

Compound No.	Antifungal Activity Parts Per Million Inhibitions of Fungus and Yeast Species: *C. albicans*	*C. tropicalis*	*A. niger*	T. *ajelloi*	*T. mentagrophytes*	*T. rubrum*
20				100	100	
136					100	
40	100	100		100	100	
35				100	16	
39				100	100	
133	100	100		8	8	8
134				100	16	
139					100	
137				100	100	
135				100	100	
142					100	
132				100	100	
138				100	100	
130	100	100		100	100	
113	100	100			100	
9					16	16
10					16	16
116					16	16
127					16	16
109					128	32
114					16	1
118					256	4
123						2
131					16	2
140						<0.5
151						1
191						8
120						1
8					8	8
16					4	2
110			128		128	64
122						32
112					128	64
153		100				

TABLE IX-continued

Compound No.	Antifungal Activity Parts Per Million Inhibitions of Fungus and Yeast Species *C. albicans*	*C. tropicalis*	*A. niger*	*T. ajelloi*	*T. mentagrophytes*	*T. rubrum*
124	100	100		100	100	8
58				100	100	100
59						100
62				100	100	100
126				100	100	100
145				100	100	100
159				100	100	100
160				100	100	100
163				100	100	100
164				100	100	100
165				100	100	100
167				100	100	100
168				100	100	100
169				100	100	100
173				100	100	100
179				100	100	100
182						100
184				100	100	100
185				100	100	100
186				100	100	100
189				100		100
187				100		100
123						16
129				16	16	8

A number of the compounds encompassed in the present invention have been found to have immunosuppressant action. Of those tested, most of these are of the 4-substituted imidazo[1,2-a]quinoxaline type described in formula I above, although a couple are of the 1-(2-acylaminophenyl)imidazole type shown in formula II. Because they exhibit this activity, they are indicated for use in the treatment of those diseases that the prior art recognizes may be helped by the administration of immunosuppressants. These include such conditions as: glomerulonephritis, serum sickness, organ transplant, rheumatoid arthritis, systemic lupus erythematosis, ulcerative colitis, chronic active hepatitis, multiple sclerosis, heterografts or homografts in burns, psoriatic arthritis, urticaria, respiratory allergies, i.e. asthma, hayfever; scleraclerma, mycosis fungoides, dermatomyositis, psoriasis and contact dermatitis (including poison ivy).

The dosage level for administering the immunosuppressants of the present invention will vary with the particular compound that is to be administered. In general, this will be at about the same level of the prior art immunosuppressants. For the most part, when the present immunosuppressants are administered orally or intraveneously, the daily dose would be in the range of about 0.1 mg. to 15 mg./per kilogram of body weight. When other mode of administration are employed, e.g. depot injections, implants, etc. the dose may be considerably higher i.e. up to about 100 mg./kg of body weight in a single injection.

The immunosuppressant activities of the compounds of this invention were determined via the hemolysin test in mice and by the delayed hypersensitivity test. The hemolysin test used is that described in *Methods in Immunology*, edited by D. H. Campbell et al, W. A. Benjamin, New York 1963 pages 172–175, and measures humeral or antibody response. The delayed hypersensitivity test measures the effect of a test compound on the ability of a subject mouse to mount a cell-mediated immune response to the antigen, Mycobacterium tuberculosis H37Ra. The mouse is sensitized to the antigen by subcutaneous administration in the base of the tail. The development of the delayed hypersensitivity response may be measured at any time beginning six days after sensitization but is usually done on the ninth day as follows: The right hind paw is injected with purified protein derivative (tuberculin) while the left hind paw (control) receives physiological saline. Both paw volumes are measured after twenty-four hours and significant increase in the volume of the right hind paw is taken as a measure of an effective delayed hypersensitivity response. All compounds were administered by the subcutaneous route.

The results of these studies are summarized in Table X below. The expression HL(ED_{50}) mg./kg. s.c. is an expression of the number of milligrams per kilogram of body weight of the drug administered subcutaneously required to reduce the antibody activity by 50% when compared with a control. In this case, the lower the HL(ED_{50}) value for a drug the more effective immunosuppressant it is.

The D.H.S. (ED_{60}) mg./kg. s.c. value appearing in column 3 is an expression of the effectiveness of the drug in reducing the edema that accompanies the cell-mediated immune response. It is a measure of the number of milligrams per kilogram of body weight of the drug administered subcutaneously which is required to reduce the edema of the cell-mediated immune response by 60% when compared to the control. Again, the lower the D.H.S. (ED_{60}) value the more effective is the drug as an immunosuppressant for the cell-mediate immune response.

TABLE X

Compound No.	HL(ED_{50}) mg/kg,s.c.	D.H.S. (ED_{60}) mg/kg,s.c
151	0.3	1.52
140	0.26	1.15
131	18	81
116	>50	56
117	>50	46
118	>50	43
109	>50	>50
110	—	50
3	50	50
66	46	>50
147	0.027	1.7
134	0.5	7.2
137	<0.125	3.2
135	0.033	0.22
142	0.20	4.2
136	2.7	>50
133	0.75	32
139	3.0	>50
138	0.72	27
127	>50	36
170	6.6	>50
150	22	>50
143	0.36	1.3
174	0.61	8.0
171	0.96	59.0
175	0.09	5.9
178	11.0	46.0
196	0.42	45.0
197	1.6	37
3	50.0	50.0
169	46	>50.0
146	0.11	3.1
153	1.2	5.7
149	0.16	8.8
126	35.0	>50.0
177	13.0	>50.0
182	1.1	—
162	13.0	—
173	—	40
159	3.0	27
181	16.0	—

TABLE X-continued

Compound No.	HL(ED$_{50}$) mg/kg,s.c.	D.H.S. (ED$_{60}$) mg/kg,s.c
180	5.6	—
183	0.39	15
158	1.0	7.6
157	0.39	12
218	1.5	25
219	2.5	>32
220	2.3	11
222	1.0	>32

>50 means that it would take more than 50 mg./kg. of drug to reduce the humeral antibody activity by 50% or to reduce edema of the cell mediated immune response by 60%. Since these values are higher than is of practical interest from a clinical point of view, no further testing was doe for these materials.

A number of compounds encompassed in the present invention display non-steroidal anti-inflammatory properties. This appears to be generally the case for the 4-substituted imidazo[1,2-a]quinoxalines of formula 1 above and the 1-(2-acylaminophenyl)imidazoles of formula II. Because of this characteristic, they are indicated for use in the treatment of diseases that the prior art recognizes may be helped by the administration of non-steroidal anti-inflammatory compounds. These include such conditions as ichthyosis, psoriasis, alopecia, atopic eczemas, etc.

The dosage level for administering the anti-inflammatory agents of the present invention may vary somewhat depending on the particular drug selected, the disease being treated and the mode of administration. In general, however, when used for topical application, the compounds are distributed in a pharmaceutical vehicle suitable for topical application. In these compositions, the anti-inflammatory agent of this invention will comprise about 0.5% to 15.0% by weight based on the total weight of the composition.

The anti-inflammatory agents of the present invention may also be administered orally, intraveneously, subcutaneously, intramuscularly, and intradermally. In these cases, the daily dosage will be in the range of from 0.5 mg. to 20 mg. per kilogram of body weight of the active anti-inflammatory agents of this invention.

The anti-inflammatory activity of representative compounds of this invention was determined by the rat paw edema assay both by local administration (Table XI below) and by oral dosing (Table XII below). For the oral dosing, the procedure of C. A. Winter, E. A. Risley and G. W. Nuss, Proc. Soc. Exp. Biol. Med. 111, 544 (1962) was employed with measurement taken four hours after the drug was administered. The local administration tests were carried out similarly except the irritant (carrageenan) and the test compound were injected simultaneously at time zero.

Tables XI and XII report the anti-inflammatory activity of the compounds tested as % difference in the edema or swelling as compared with the control. These Tables also give the response in many instances of more than one dose level of the same drug.

TABLE XI

	Rat Paw Edema Assay, Local Administration (injected directly into paw) % Difference from Control			
Compound No.	1μg	10μg	100μg	100 mg/kg
148	−32.6	−53.5	−14.3	−39
109	−30.8	−3.9	+31.6	
114	−68.2	−30.0	−131.6	
117				
110				−74
122				−61
49				−35
7				−22
51				−57

TABLE XI-continued

	Rat Paw Edema Assay, Local Administration (injected directly into paw) % Difference from Control			
Compound No.	1μg	10μg	100μg	100 mg/kg
140				−78

TABLE XII

	Rat Paw Edema Assay, Oral Dosing %Difference from Control	
Compound No.	100 mg/kg	400 mg/kg
Indomethacin	−65	
phenybutazone	−76	
Aspirin	−57	
114	−61	
110	−43	
122	−61	
148	−52	
49	−35	
7	−52	
51	−57	
140	−35	
131	−52	
10	−30	
39	−50	
133	−17	
137	−26	
112	−17	−68
111	−43	
121	−61	
147	−39	
134	−43	
139	−22	−25
132	−76	
150	−30	
144	−26	
115	+70	−25
117	−7	−18
123	0	−50
116	+104	−18
136	−9	−25
8	−22	−13
29	−24	−25
14	−52	
20	−59	
38	−41	
57	−35	
50	−20	−33
45	−33	
40	−43	
35	−50	
37	−35	
18	−28	
15	−24	−5
55	−26	
52	−26	
2	−26	+43
23	−46	
25	−30	
30	+9	−33
36	−7	−68
42	−9	−25
24	−17	−25
109	−17	
71	−22	
75	−30	
68	−26	
73	−22	
128	−39	
129	−30	

What is claimed is:

1. A method for inhibiting fungal growth comprising contacting a fungus sensitive thereto with an amount sufficient to inhibit the growth of such fungus of an imidazo[1,2-a]quinoxaline substituted at the 4-position by a hydrogen, an alkyl group of from 1 to 17 carbon atoms, 9-decenyl, a trifluoromethyl group, a benzyl group, a cycloalkyl group of from 4 or 6 carbon atoms, a styryl group, a phenyl group, and a phenyl group substituted by methyl, chloro, nitro or amino, in a suitable carrier therefor.

2. The method for inhibiting fungal growth according to claim **1** wherein said imidazo[1,2-a]quinoxaline is present in an amount of from about 0.5% to 10% by weight.

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